David Mahaffey

EXHIBIT H
FILED UNDER SEAL

EXPERT REPORT OF DAVID MICHAELS, Ph.D., M.P.H.

Diana Hc¡fmann et al. v. Syngenta Crop Protection, LLC, et al.
No. 17-L-517
Circuit Court for the Twentieth Judicial Circuit
St. Clair County, Illinois

July 10, 2020

I. QUALIFICATIONS AND METHODOLOGY

I have spent my entire career in the field of public health, serving as a senior public health official, professor and researcher. I hold a BA in history from the City College of New York, an MPH (Masters in Public Health) in epidemiology from Columbia University and a PhD in socio-medical sciences, also from Columbia University. I began my public health career at the Montefiore Medical Center and the Albert Einstein College of Medicine (AECOM) in 1977, assisting in an occupational health training program for medical students, a program I later went on to direct. I earned my first faculty appointment, at the rank of Lecturer, in the Department of Epidemiology and Social Medicine at AECOM in 1980. I have held a faculty appointment in the Department of Community and Preventive Medicine of the Mount Sinai School of Medicine since 1993, earning the rank of Professor in 2001. Both AECOM and the Mount Sinai School of Medicine are located in New York City.

My primary faculty appointment at the present time is Professor and Vice Chairman, Department of Environmental and Occupational Health, at the George Washington University Milken Institute School of Public Health, in Washington DC. I am also a member of the Department of Epidemiology.

In 1998, I was nominated by President Bill Clinton, and then unanimously confirmed by the U.S. Senate, to the office of Assistant Secretary for Environment, Safety and Health, U.S. Department of Energy (DOE). I served in that position through January 2001. In this position, I had primary responsibility for protecting the health and safety of more than 100,000 workers, the neighboring communities and the environment surrounding the nation's twelve nuclear weapons production and testing facilities and 21 national laboratories and technology centers.

In 2009, I was nominated by President Barack Obama, and then unanimously confirmed by the U.S. Senate, to the office of Assistant Secretary for the Occupational Safety and Health Administration, U.S. Department of Labor. I served in that position through January 2017 and was the longest serving head of OSHA in the agency's history.

My contribution to the field of public health has been recognized by my peers. In 1984, I was awarded the Jay S. Drotman Memorial Award, given by American Public Health Association to the outstanding public health professional under the age of 30. In 2000, I was given the Samuel Gompers Award by the International Association of Industrial Accident Boards and Commissions. The following year, I was honored with the American Public Health Association's David P. Rall Award for Advocacy in Public Health. In 2006, I was given the Scientific Freedom and Responsibility Award by the American Association for the Advancement of Science and the John P. McGovern Science and Society Award given by Sigma Xi, the Scientific Research Society. I am also a recipient of the American Conference of Governmental Industrial Hygienists' William D. Wagner Award.

I have published numerous epidemiologic studies on the health of workers exposed to toxic substances. A fundamental component of these studies is examination of the historical literature. The purpose of this is to identify the exposures that occurred in different periods of time, as well as what was known by the scientific community at the time the exposures occurred. This often entails examination of studies and reports published over many decades; in one study I published

on the mortality experience of lead-exposed typographers, I reviewed exposure data from as early as 1942, as well the debates occurring in the scientific literature on the relationship of toxic exposure and disease from the 1930s.

I have written extensively on issues related to the integrity of scientific information that serves as the basis of public health and environmental regulation. I am the author of Doubt is Their Product: How Industry's Assault on Science Threatens Your Health (Oxford University Press, 2008) and The Triumph of Doubt: Dark Money and the Science of Deception (Oxford University Press, 2020). My studies and articles have been published in Science, JAMA, the International Journal of Epidemiology, the American Journal of Public Health and other scientific journals.

A copy of my curriculum vitae is attached as Exhibit A.

I have been engaged by the law firm of Korein Tillery to offer my opinion regarding corporate stewardship, the responsibility of the manufacturers of potentially toxic products to be truthful about scientific findings relating to their products, and how Defendants failed to live up to that responsibility here.

The methodology I employed in preparing this report involved reviewing primary sources, including articles published in the scientific literature over the course of several decades as well as memos, emails and other documents, in order to trace the Defendants' conduct in connection with manufacture, formulation and sale of paraquat. I also read and relied on the reports of two other experts engaged in this same matter.

I analyzed the information that was reported to the scientific community and examined contemporary records from the Defendants to determine how they reacted to the information being reported.

II. CORPORATE "PRODUCT DEFENSE" STRATEGIES

The public is largely unaware of the depth and scope of corporate deception involving the scientific inquiry into whether exposure to products cause disease. Those in the business of making toxic products know the public is in no position to distinguish good science from bad and use this to their advantage. I have spent my much of my career studying the practices by which corporations defend toxic products. This report presents a description of those methods and how they been employed to defend paraquat, an extremely toxic chemical, and convince the public and public health regulators that it is less dangerous than it actually is.

When faced with concern that a profitable product is harmful to humans, it is rare for a corporation to actually try to determine whether the concerns are justified in fact, and, if so, even rarer for them to stop making or selling the product. Instead, corporations typically follow a product defense playbook penned in large part long ago by the tobacco industry in defense of cigarettes and smoking.

By 1954, the science regarding the connection between lung disease and smoking should have prompted every scientist and every tobacco executive to assume that cigarettes are killers and treat them accordingly unless and until further research proved the existing science wrong.

Instead, the tobacco industry worked tirelessly for decades to promote the studies that would support their preordained conclusions and suppress any findings that suggested otherwise. When you are defending a product that harms or even kills people, real science is your enemy.

The asbestos industry played the very same hand to cover up the dangers associated with its toxic products. By the 1930's, anyone and everyone in the asbestos industry could have known, should have known, and almost certainly did know that asbestos causes lung disease because the evidence was simply overwhelming. But instead of taking responsibility and doing something to protect users from further harm and compensate users already harmed, the asbestos industry followed a playbook similar to that of Big Tobacco. They denied, they shifted blame and they obfuscated the science until they could no longer do so.

Since then, countless industries have used such uncertainty campaigns to stave off liability and regulation with regard to the health effects of toxic chemicals, prescription drugs, food and beverages. Misinformation campaigns unite questionable science with a full-court press of public relations. The industry under attack publishes studies performed by mercenary scientists, who are paid to reach the desired conclusions of their masters, in vanity journals that are "peer reviewed" in name only by other industry-friendly scientists. They manipulate existing independent science to either discredit it or the scientists behind it or to skew the results to favor industry.

The point of all this scheming is not to win the war and prove dangerous products safe. The name of the game is to sow confusion, create doubt and manufacture uncertainty with the public, regulators, judges and juries in order to buy time so they can continue to make profits and avoid having to compensate victims in the short term. Delay is a victory for industry.

What I am describing here, and what I have written about extensively, is public relations disguised as science. Industry employs a range of strategies to achieve their goal of confusion (and delay). Several of these strategies are described below.

A. Apply a reasonable doubt standard to products

First, manufacturers try to hold anyone trying to prove that Chemical X causes Disease Y to something akin to the prosecutor's standard of proof in a criminal trial, i.e., guilt beyond a reasonable doubt. But causation in civil tort cases is evaluated under the far less strict preponderance of the evidence standard. Regulatory agencies make decisions to protect the public based on the best evidence available at the time, and should not wait for certainty if it means delaying protecting the public's health. Further, uncertainty is inherent in science. Scientists know there is no need for and that they can almost never obtain proof beyond a reasonable doubt. Absolute certainty in science is rare; uncertainty is the norm, not the exception; and scientists accordingly base their judgments on the weight of the evidence because in many instances they have no other choice. Uncertainty does not mean the science is flawed. The absence of evidence does not mean evidence of absence.

And of all scientific uncertainties, few are more complex than understanding the causes of human disease. There are several reasons for this. It is unethical and immoral for scientists to expose humans to toxic chemicals to see whether and at what dose they cause disease. Further,

some diseases occur naturally even without exposure to any toxin. And most cases of environmentally-caused disease are clinically identical to ones that would have occurred had there been no exposure. Thus, it is often not possible to say with absolute certainty that a chemical exposure was responsible for a particular case of disease. In many cases, all the best science can provide is a probability statement. The tobacco industry took advantage of the fact that some people who get lung cancer have never smoked and that not all smokers get lung cancer to create doubt as to whether cigarettes were in fact a cause of lung cancer.

The demand for absolute scientific certainty is both counterproductive and futile. The manufacture and magnification of scientific uncertainty endangers both the public's health and systems intended to compensate victims. Scientists therefore use the best evidence available and do not demand certainty where it does not and cannot exist.

B. Presume a product innocent until proven guilty

Second, industry seeks to take advantage of the "innocent until proven guilty" presumption afforded criminal defendants. But toxic chemicals are not persons and have no constitutional rights. Further, why should any chemical that can reasonably be predicted to cause harm to humans be given a presumption of innocence? In a perfect world, industry would be required to establish the safety of their products before they are allowed to profit from their sale. In any event, waiting for proof of harm before taking action will too often permit harm to occur. This is particularly true when the disease at issue has a long latency period. Corporations know they can profit from sale of their harmful products for many years before any symptoms of the disease manifest.

C. Fail to conduct product studies

Third, industry does as little as possible (sometimes nothing) to find the truth. Because industry does not want to know the truth, it simply fails to conduct studies that might have ascertained the truth. Corporations often perform inadequate safety testing on their products (and conceal the unfavorable results they do have). They have basically adopted a "don't ask, don't tell" policy. Epidemiology is the "gold standard" of proving causation of disease in humans. Yet the manufacturers of toxins rarely, if ever, conduct a full-scale epidemiological investigation of their products, likely because they know what the research would reveal. Nothing is done until there are a sufficient number of "bodies in the morgue" and the manufacturers are forced to do something. To add insult to injury, industry then uses this *self-imposed* lack of scientific "certainty" to defend itself against regulation and liability. Time after time corporations claim a "lack of evidence" as reason for inaction, when in fact *they* are responsible for that lack of evidence.

D. Attack and demand perfection of others' research

Fourth, industry demands perfection from all unfavorable scientific studies. However, even imperfect studies have value, and they are often all we have. As Voltaire said, "the perfect is the enemy of the good." Human health should not take a back seat to the pursuit of perfect science.

Further, industry's attacks on the existing science are predictable and largely bogus. The easiest way to discount unfavorable science is the process of "reanalysis." Rather than creating their own studies and gathering their own data, industry demands someone else's raw data and manipulates them to reach the conclusion they want in a ploy known as "data dredging." Once a study's results

are known, it is easy to design a reanalysis to make those results (if they show a positive association) disappear. If parameters are changed or new cut-off points between categories are selected, statistically significant differences suddenly evaporate and risk estimates are suddenly reduced. But in epidemiology, changing your methods after you have seen your results is extremely bad form, especially if it changes those findings, because it raises questions as to whether you are manipulating the data to get the result you want. However, industry knows that most people are not schooled in proper epidemiological methodology and that reanalyzing a study's raw data to change its results is a very effective way to neutralize the study's conclusions.

Epidemiology is a sitting duck for uncertainty campaigns, because study design is complicated and depends on judgment calls (and integrity) at every step along the way. Non-epidemiologists may not realize that epidemiological studies are intentionally skewed toward *rejecting* a given hypothesis (*i.e.*, Chemical X causes Disease Y), so the fact that a study failed to prove a hypothesis does not at all mean the hypothesis is thus disproved. It is far more difficult to find a false positive result than a false negative one.

Further, it is hard to obtain data on nonfatal diseases, like Parkinson's disease. Using mortality data will miss most cases of the disease in instances where people do not die from it, like Parkinson's disease. Because of the lack of data, science is thus less able to detect patterns of excess risk of nonfatal disease due to the very nature of the disease itself.

Animal studies conducted in laboratories are also subject to attack. When people are exposed to numerous chemicals at their place of work, it is difficult to parse the respective effects of the various chemicals. This is an instance in which scientists make judgments by using information they import from other sorts of studies, particularly animal studies.

But the go-to industry attack on animal studies is that because they involve too high a dose of the toxin, *i.e.*, a dose a human would never be exposed to in the real world, the results of animal studies cannot validly be extrapolated to the human experience. This argument ignores practical realities. When toxicologists design animal studies, they deliberately use as high a dose as possible that will not kill the animal because they cannot perform a study large enough to see the effect of the toxin at a lower dose. For instance, if an air pollutant is suspected to cause cancer in one of every thousand people, you would need a study of a thousand animals. Scientists cannot practically conduct studies with thousands of animals, so they use high dose in a smaller number of animals instead, knowing that a substance that does not cause, for instance, cancer does not cause cancer ever, not even at the highest doses. In short, there is nothing inherently wrong with animal studies and the reality is that for many chemicals, animal studies provide virtually everything we know about their toxicity.

Another common line of attack is to demand animal studies if the epidemiological studies are bad and vice versa. In short, no proof and no amount of proof is ever good enough for corporate producers of the chemical in question.

Finally, industry will conduct meta-analyses to combat unwanted science. A meta-analysis combines and analyzes the combined data from several already completed studies on the theory that more data leads to more accurate results. However, meta-analyses are subject to the "garbage in/garbage out" principle. In other words, if you build a meta-analysis with flawed studies,

you get a flawed result. A time-honored industry recipe for countering the results of a well-conducted study (that doesn't favor them) is to mix the good study with several weak or poorly designed ones to arrive at a "no findings" conclusion. The added value of this charade is that the investigator and sponsor can claim that the new meta-analysis includes the *entire literature* and therefore trumps the result of that one pesky study. In this regard, industry turns the basic scientific principle that conclusions are reached based on the "weight of the evidence" on its head to create uncertainty and doubt.

E. Suppress research

Fifth, industry suppresses research when the results are adverse to their interests. Suppression of research has been a recurring problem with privately sponsored research. Suppressing adverse results can be achieved with discretionary judgments that are not technically illegal. For example, industry can abort research before it is completed and claim limited resources or some purported design flaw in the study impelled the decision. For research that is completed, industry can justify withholding the results based on discretionary judgments that the research design or reporting was incomplete or flawed in some way or that follow-up research is needed to confirm or validate the findings. All of these judgment calls are difficult to question from the outside. Industry sometimes contractually reserve the right to suppress publication of the research they fund and will not hesitate to use this right if the study results are adverse to their interests.

F. Distort the scientific picture

Sixth, industry distorts the scientific picture by publishing their own "litigation science" -- manufactured research that has nothing to do with advancing the scientific inquiry and instead is done for the purpose of convincing judges and juries their products do not harm people. Not surprisingly, nearly all industry-funded studies reach conclusions favorable to industry.

The most common type of study in this regard in the strategic literature review – a survey of the existing literature in which the authors review the evidence, commenting of the purported strengths and weaknesses of the studies reviewed. The authors weigh the evidence reviewed and provide a conclusion about the likelihood that a specific exposure causes a specific outcome, or about the level of exposure necessary to cause the outcome in questions. A common conclusion of these strategic literature review is that that the evidence reviewed is inconsistent and more research is needed before a definitive conclusion can be reached.

These "studies" are then published in "vanity journals" -- conflicted journals that publish questionable science from industry and their hired guns for the purpose of giving the studies credibility. Industry knows they need the imprimatur of "peer review" to establish credibility for their studies and reanalysis. They obtain this coveted seal of approval by establishing vanity journals that present themselves to the unwary as independent sources of information and science, but the peer reviewers are carefully chosen, like-minded corporate consultants sitting in friendly judgment on studies that are structured to influence a regulatory proceeding or court case. Science compiled or conducted for the purposes of litigation should be inherently suspect.

In addition to strategic literature reviews, industry will often commission studies that are designed or conducted in ways that make it very likely they will produce favorable results. They

look at small groups of workers over short periods of time. They include a larger group of non-exposed workers. They manipulate cohort studies by including only workers whose exposures began less than 20 years ago, taking advantage of disease latency. They study only a population of workers, which is inherently biased because workers are healthier than non-workers in general. They make misclassification errors regarding exposure, *i.e.*, a person with higher exposure is classified as low or a person with lower exposure is classified as high, both of which errors tend to lower the degree of risk than in fact exists. They give undue weight to the types of evidence that support their claims. For instance, in a dataset including workers and bystanders, they heavily weight the bystander data because there are more of them, thereby diluting the effects seen in workers. They dilute the results by lumping groups of workers with different exposures together. And, of course, one of industry's favorite techniques is to blame confounders (or unaccounted factors that are not the product at issue).

Industry studies are motivated by principles other than finding the truth. Their goal is to create uncertainty—"Maybe there is another cause for disease? What about people who were exposed but did not get the disease? Maybe different forms of the product do not cause the harm at issue? Maybe skin exposure is less harmful than inhalation?" The list goes on. None of these inquiries are meant to advance science, but rather to make the issue look so complicated that additional research must be done before any conclusions can be drawn. Again, the goal is to buy more time.

One might ask, if these studies are so obviously flawed, what use could they possibly be to industry? The unfortunate fact is that studies of no value whatsoever in the scientific arena can be quite valuable for corporate defendants in the courtroom. A jury might be impressed by a one-hundred-page "peer reviewed" article claiming that all of the existing studies are "junk science," whereas the industry's own "sound science" creates sufficient doubt as to whether the toxin caused the injury. Remember, industry does not have to prove anything – just manufacture sufficient doubt. And sponsorship by litigation parties leads to an imbalance in the literature—data synthesis exercises, data reanalysis, and exposure estimations predominate.

Not all industry-funded scientists are corrupt, but even honest scientists are subject to a psychological phenomenon called "motivated reasoning." Being paid by industry changes the way a scientist looks at the scientific literature. As Upton Sinclair put it: "It is difficult to convince a man of something if his salary depends on him not believing it." The public believes science is straightforward, but the reality is that the desire to please the sponsor changes how the results are reported. Conflicted science is not valid, because no matter who performs the study, those paid for by a private sponsor tend to deliver the results the sponsor wants. The studies are typically (and improperly) structured by starting with the answer industry wants and figuring out the best way to support it. The phenomenon is so well-known that it has been given a name – the "funding effect" -- referring to the close correlation between the results desired by a study's sponsors and the results reported.

In short, any science generated by industry is inherently suspect and should, unfortunately, be viewed with suspicion.

G. Shift blame

Seventh, industry shifts blame to anything or everything other than their product, including the victims themselves. The existence of other risk factors, of course, does not exonerate your product, but it can confuse the public. The tobacco industry tried to shift blame for lung cancer onto many other risk factors, real and imagined. The lead industry for many years denied proof that lead causes a host of serious health issues and instead blamed irresponsible parents who allowed their children to eat the paint peeling from the walls of poorly maintained homes.

Where the victims are workers, industry will try to shift responsibility to the injured worker by accusing them of not using proper personal protective equipment. The "hierarchy of controls" is the bedrock principle of industrial hygiene and requires that you modify the work environment rather than the worker. In other words, the hierarchy prioritizes engineering controls over less effective personal protective equipment like respirators. Respirators are in fact the last choice, not the first, for several reasons: 1) they are less effective than other environmental techniques (wetting, vacuum); 2) they are hot and unpleasant; 3) communication is difficult while wearing a respirator presenting an altogether different safety issue; 4) workers with heart/lung issues cannot wear respirators safely; and 5) the wearer must be clean-shaven because facial hair breaks the seal.

H. Focus on dose and exposure levels when causation is no longer plausibly deniable

Once the industry is no longer able to plausibly deny causation, they turn their uncertainty campaign to the question of dose, *i.e.*, what level of exposure creates the risk at issue. Industry's typical last ditch effort is to claim the disease effect is real only at the highest levels of exposure, while lower levels yield no increased risk. This is false, but hard to rebut because it can be a difficult challenge to find a statistically significant excess risk of disease at low levels of exposure.

I. Use secrecy orders and abuse attorney-client privilege to hide the truth from the public

Ninth, industry uses secrecy orders and abuses the attorney-client privilege to keep all of this under wraps. The tobacco industry famously used the particularly shady practice of funding conflicted science through a law firm so they can claim the attorney-client privilege.

And industry does not do all of this alone. An entire cottage industry of "product defense firms" has evolved over the years. Their business model is straightforward. They profit by helping corporations minimize public health and environmental protection and fight claims of injury and illness. In field after field, year after year, the same handful of individuals and companies comes up again and again. The entire point of what they do is to clog the machinery and slow down the process. The work of the product defense industry looks impressive – carefully manicured reports and reanalysis, captured journals full of "peer reviewed" articles, and captured think tanks hiring out their ad hoc advocacy sow uncertainty across a range of issues. It is all a ruse, but it is regrettably an accepted part of the game. Work by scientists employed by firms specializing in product defense and litigation support must be seen for what it is: advocacy, rather than science.

Exponent is one such product defense firm. While some may exist, I have yet to see an Exponent study that does not support the conclusion needed by the corporation/trade association that

is paying the bill. In the case of paraquat and Parkinson's disease, an Exponent scientist, along with other product defense consultants, were members of Syngenta's "External Epidemiology Expert Team" and in fact produced and published strategic literature reviews and studies that questioned the causal connection between pesticide exposure and Parkinson's disease.

THE ILLINOIS CONSUMER FRAUD ACT

I have been asked to assume that in consumer cases in Illinois, a consumer needs to show "a deceptive act or practice by the defendant" and that the defendant intended the consumer to rely on the deception." I have considered an act to be "deceptive" if it creates the likelihood of deception or has the capacity to deceive. Omissions, like acts of commission, can be a deceptive act or practice if the information not disclosed is the kind upon which a buyer would be expected to rely in making a purchase decision.

I have also been asked to assume that another way a consumer may establish a case is to show that the defendant's "practice offends public policy" or that "it is immoral, unethical, oppressive, or unscrupulous" and/or that "it causes substantial injury to consumers." A practice may be unfair because it satisfies one of those three criteria to a strong degree or meets all three to a lesser degree. Public policy is found in statutes, regulations, and common law.

The statutory and regulatory provisions I have considered as a reflection of public policy are:

- Article XI of the Illinois Constitution of 1970, Environment, Section 1, Public Policy - Legislative Responsibility, provides that:

  > The public policy of the State and the duty of each person is to provide and maintain a healthful environment for the benefit of this and future generations. The General Assembly shall provide by law for the implementation and enforcement of this public policy."

- Article XI of the Illinois Constitution of 1970, Environment, Section 2, Rights of Individuals, provides that:

  > Each person has the right to a healthful environment. Each person may enforce this right against any party, governmental or private, through appropriate legal proceedings subject to reasonable limitation and regulation as the General Assembly may provide by law.

Regulatory Framework: EPA Reporting Requirements

- FIFRA § 6(a)(2), 7 U.S.C. § 136d(a)(2)

  > If at any time after the registration of a pesticide the registrant has additional factual information regarding unreasonable adverse effects on the environment of the pesticide, the registrant shall submit such information to the Administrator.

7 U.S.C. § 136(bb) Unreasonable adverse effects on the environment

> The term "unreasonable adverse effects on the environment" means (1) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 346a of title 21. The Administrator shall consider the risks and benefits of public health pesticides separate from the risks and benefits of other pesticides. In weighing any regulatory action concerning a public health pesticide under this subchapter, the Administrator shall weigh any risks of the pesticide against the health risks such as the diseases transmitted by the vector to be controlled by the pesticide.

- When Congress amended the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) in 1972, it adopted a broad reporting requirement—FIFRA § 6(a)(2).[1]

- "Since approximately 35,000 pesticide products are currently registered with EPA, it is not difficult to understand why Congress imposed such a duty to keep the Administrator informed on registrants." 43 Fed. Reg. 37611, 37612 (August 23, 1978).

- FIFRA Section 14(b) authorizes criminal prosecution of a registrant who knowingly violates FIFRA and imprisonment of up to one year. 7 U.S.C. § 136l(b)(1)(A).

- Sections 12(a)(2)(N) & (Q) make it unlawful for a registrant "to fail to file reports required by this subchapter" or "to falsify all or part of any information relating to the testing of any pesticide ..., including the nature of any ... observation made, or conclusion or opinion formed, submitted to the Administrator, or that the person knows will be furnished to the Administrator." 7 U.S.C. § 136j(a)(2)(N) & (Q).

- EPA regulations require registrants to report a wide variety of information. Information that "is relevant to the assessment of the risks or benefits of one or more specific pesticide registrations currently or formerly held by the registrant" is mandatorily reportable. 40 C.F.R. § 159.158(a).

- Information is "relevant to the assessment of the risks or benefits," and reportable under 40 C.F.R. § 159.158(a)(1)-(3), if it includes the conclusions or opinions of a person:

  1) Who was employed or retained (directly or indirectly) by the registrant, and was likely to receive such information.
  2) From whom the registrant requested the opinion(s) or conclusion(s) in question.
  3) Who is a qualified expert as described in § 159.153(b). [2]

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[1] Codified at 7 U.S.C. § 136d(a)(2).

[2] Section 159.153(b) provides in relevant part:

> *Qualified expert* means one who, by virtue of his or her knowledge, skill, experience, training, or education, could be qualified by a court as an expert to testify on issues related to the subject matter on which he or she renders a conclusion or opinion. Under Rule 702 of the Federal Rules of Evidence, a person

- The EPA in 1998 provided guidance for Section 6(a)(2) reporting, explaining the crucial importance of expert opinion to its work: "As a general matter, the Agency frequently relies on the 'weight of evidence' in making pesticide regulatory decisions, and it considers expert opinion that tends to confirm or validate otherwise reportable information. In this context, expert opinions can play an important role in Agency decision-making."[3]

- Another EPA regulation requires reporting of certain scientific studies, discontinued studies, human epidemiological studies, and human exposure studies. 40 C.F.R. § 159.155. Toxicological studies are among the scientific studies specifically addressed.

- Section 159.165 makes mandatorily reportable adverse findings in toxicological studies notwithstanding similar findings of prior studies "if, relative to all previously submitted studies, they show an adverse effect":

  - in a different organ or tissue of the test organism,
  - at a lower dosage,
  - after a shorter exposure period,
  - after a shorter latency period,
  - at a higher incidence or frequency,
  - by a different route of exposure,
  - in a different ***species*** strain, sex, or generation of test organism. 40 C.F.R. § 159.165(a)(1)(i)-(v).

- The EPA also has a catch-all regulation that makes "other information" mandatorily reportable. A registrant must submit "information other than that described in § 159.165 … if the registrant knows, or reasonably should know, that if the information should prove to be correct, EPA might regard the information alone or in conjunction with other information about the pesticide as raising concerns about the continued registration of a product or about the appropriate terms and conditions of registration of a product." 40 C.F.R. § 159.195.

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may be qualified as an expert on a particular matter by virtue of "knowledge, skill, experience, training, or education." In general, EPA wants registrants to report information when a person has relevant expert credentials, e.g., a medical doctor giving a medical opinion, a plant pathologist giving an opinion on plant pathology, etc. (emphasis added).

[3] April 3, 1998 Guidance on Final FIFRA Section 6(a)(2) Regulations for Pesticide Product Registrants at 8-9 (attachment to EPA Notice 98-3) (available at https://www.epa.gov/sites/ production/files/2014-04/documents/pr98-3.pdf).

As the EPA has explained for forty years:

> [P]esticide regulatory decisions involve much more than whether or not a pesticide should be registered at all; the Administrator is required to make a number of decisions about the terms and conditions of registration which are not expressly stated in terms of "unreasonable adverse effects on the environment." Among these are decisions concerning the pesticide's labeling and packaging, and decisions concerning whether additional restrictions beyond labeling should be imposed. ... [T]he Administrator has the option of changing some or all of these terms or conditions after registration, as remedies short of outright cancellation, in situations where he determines that without such changes, the pesticide would generally cause unreasonable adverse effects.

43 Fed. Reg. 37611, 37613 (August 23, 1978). "If the information would be relevant to an *Agency* decision on the continued registration of the pesticide or to the proper terms and conditions of the pesticide's registration, and the other requirements of section 6(a)(2) are satisfied, the registrant is required by section 6(a)(2) to submit the information to the Agency." *Ibid.* (emphasis in original)

SYNGENTA HAS ADMITTED ITS CORPORATE RESPONSIBILITY REGARDING PRODUCT SAFETY

In its deposition, Syngenta admitted the following:

- Companies involved in making products subject to regulation have the duty to be truthful with regulators. Botham: 490; Botham: 598.
- When in doubt, the responsible thing is to report findings to regulators. Botham: 287-288.
- Companies who are in the business of manufacturing or distributing pesticides have a duty to act responsibly to ensure the health and safety of their pesticides. Botham: 598.
- A company in the business of manufacturing or distributing pesticides has a duty to consumers to disclose serious harms caused by those pesticides. Botham: 599.
- A company in the business of manufacturing or distributing pesticides has a duty to conduct scientific research with the highest standards of professionalism and good science. Botham: 599.
- Syngenta scientists are ethically required to share their scientific findings about paraquat. Botham: 490.
- A company in the business of manufacturing or distributing pesticides has a duty to be transparent with its research findings and to publicly disclose research results of significance in an objective and accurate way. Botham: 600.
- A company in the business of manufacturing or distributing pesticides has a duty to communicate information concerning health, safety and toxicity in a timely and responsible manner. Botham: 600.
- Transparency in science is critical, especially for heavily-used products and serious health effects. Botham: 291-93.
- If Syngenta has information that paraquat is a neurotoxin, it would be improper, unethical and dishonest to withhold that information from regulators and the public. Botham: 491-93..

ANALYSIS

III. Syngenta's Corporate Defense of Paraquat Follows the Corporate Template

A. For decades Syngenta treated paraquat as innocent until proven guilty

In undertaking my investigation and analysis of this case, I relied on the exhaustive work of two scientists who have read and carefully analyzed a large number of Defendants' documents obtained by Plaintiffs' counsel through the litigation process. Dr. William Farone and Dr. William Mobley have done an extremely thorough probe of these documents from two distinct and separate approaches. They have reduced their findings and conclusions into reports which I have read and found to be extremely logical and comprehensive. I have relied on those reports in reaching my own opinions in this case. The reports of their findings and conclusions are the same type of analysis that I have typically relied upon in my professional capacity in the past.

In addition, several corporate witnesses from Syngenta and Chevron have already testified under oath by deposition on behalf of those companies. I have likewise relied on several statements of fact made by those corporate witnesses. Plaintiffs' counsel have prepared a Fact Summary of extracted statements of fact from these depositions which I have also referred to and relied on.

1. Defendants knew paraquat was a powerful redox cycler and should have established it was safe for long-term use before putting it on the market.

a. ICI and Chevron's knowledge before selling paraquat

Before they started selling paraquat in the United States, ICI and Chevron knew that paraquat was an effective herbicide because of its redox properties. 2/25/20 Botham Vol. I Tr. at 90-91; 6/25/20 Patterson Vol. IV Tr. at 90, 148-49. "Redox" is a combination of "oxidation" and "reduction," referring to a chemical reaction that can kill living cells by creating "oxidative stress." Paraquat is also toxic to animals and humans, killing their cells in the same way as it does plants—oxidative stress due to redox cycling. Botham I at 91, 212-13. These facts should have led ICI and Chevron to investigate whether paraquat was safe for human long-term use before they marketed it. But ICI and Chevron conducted only limited toxicity testing before marketing paraquat. And even those studies demonstrated paraquat's potential for long-term neurotoxic harm (i.e., harm to the central nervous system).

For example, a 1963 ICI dermal toxicity study in rabbits with paraquat showed symptoms readily referable to the brain. These symptoms were indicative of possible central nervous system effects, but ICI investigated no further. Mobley Report at 8-9 (noting changes in activity levels, tremors, increased salivation, incoordination and weakness). Botham I at 215. By the time ICI put paraquat on the market, it knew that paraquat had the potential to redox cycle in any human tissue, especially in oxygen-rich sections of the brain. Botham I at 100, 174. Given ICI'S knowledge of paraquat's oxidative stress properties, that oxidative stress damages cells, and that oxygen-rich tissue like the brain is especially sensitive to oxidative stress, further investigation was essential. But ICI did not even examine the rabbit brain tissues for evidence of tissue toxicity or paraquat residues. Mobley at 9. They should have done so. They should also have conducted follow-up studies to examine whether paraquat posed any long-term or chronic risks to

the central nervous system. Mobley at 9. Had they performed the studies, it is clear what they would have confirmed.

A 1964 ICI study in dogs showed changes in brain tissue integrity. Mobley at 10. Although the rabbit study had revealed potential central nervous system and neurobehavioral effects, the investigators in the dog study failed to note motor function or other neurobehavioral effects. They also failed to examine neurons in the brain regions where effects had been seen in the rabbit. *Ibid.* As with its rabbit studies, ICI should have followed up with long-term, chronic neurotoxicity studies to establish that paraquat was safe before putting it on the market. Instead of performing the kinds of long-term neurotoxicity studies in animals that were indicated, ICI and Chevron decided to make human guinea pigs out of paraquat users and wait to see what brain injuries would result.

b. Early period after paraquat sales begin

ICI and Chevron learned more about paraquat's neurotoxic potential after they began selling paraquat in the United States, but they ignored those data, too. They conducted field studies of agricultural workers who applied paraquat and learned the chemical could be detected in workers' urine. In 1969, an ICI scientist named Swann published the results of two exposure studies (field trials conducted in Malaysia in 1965 and 1967) designed to examine exposure under real world conditions. SWANN (1967); 6/22/20 Ouzts Tr. at 47-54; *see also* Patterson IV at 14-17. Some paraquat was detected in every worker's urine at some point during the 12-week 1965 study. SWANN; Ouzts Tr. at 47-54; Patterson IV at 28-29. This meant when paraquat is used as intended, exposure is systemic. Mobley at 26. Paraquat could thus be carried to the worker's brain through the bloodstream. And from 1968 on, ICI and Chevron knew from numerous *post mortem* examinations of people who had died from acute paraquat poisoning that there were changes and signs of damage to various areas of the brain. Botham I at 202-03; 3/5/20 Patterson Vol. II Tr. at 295; 313-314; 336-37. Paraquat was also found in the victim's brains. *See also* Patterson II at 316, 321, 326-27, 352.

This early knowledge of paraquat residues in urine samples and the human brain stood as clear proof that paraquat gets into the brain. It was more than just a red flag—it was a mandate to ICI and Chevron to expand their human exposure studies. Follow-up studies should have been conducted to assess workers longitudinally for signs of general health effects, including neurological health, studies of motor performance and cognition. Mobley at 27. Furthermore, a robust epidemiological program to evaluate the general and neurological health effects and extent of exposures of a larger population exposed to paraquat as a result of living on or near land treated with paraquat should have been undertaken. *Ibid.* Neither ICI nor Chevron undertook these studies, but both could have. For the 21-year period between 1965 and 1986, Chevron could have designed an epidemiological study that monitored paraquat users long term to determine paraquat's effect on their health. Patterson Tr. at 129.

Through the 1970s and 1980s, ICI and Chevron performed a number of short-term toxicity studies and residue analyses in various laboratory species. Toxicity studies consistently found effects in the central nervous system. Not only did residue studies demonstrate that paraquat reached the parts of the brain unprotected by the blood brain barrier, but they also showed that paraquat

crossed the barrier and entered the midbrain. A number of independent paraquat toxicity and residue studies were also published over this time. Some of these also showed potential neurotoxicity, including one that showed effects on motor neurons. As this body of evidence mounted, Chevron and ICI turned a blind eye to paraquat's very likely neurotoxicity. And at no time did Chevron or ICI warn paraquat users of these risks or disclose that no neurotoxicity analysis had been undertaken. *See generally* Mobley and Farone Reports and Fact Summary.

c. Long-term toxicity tests

After having marketed paraquat in the U.S. for ten years, scientists at both ICI and Chevron admitted they had done no long-term toxicity studies to understand paraquat's neurotoxic potential. In a 1975 correspondence, Drs. Fletcher (ICI) and Cavalli (Chevron) discussed the potential for paraquat to injure the central nervous system. Mobley at 38-39. They agreed no long-term studies of paraquat's chronic effects on the central nervous system had been done. *Ibid.*; *see also* Patterson at 305; Botham at 198. Dr. Cavalli noted only a few chronic toxicity studies existed at all, and these were "old" and some were "poorly done." Mobley at 41; Botham at 198. Nevertheless, Dr. Fletcher advised Dr. Cavalli that ICI would not undertake chronic toxicity studies with paraquat. Mobley at 41.

It was not until several years later that ICI began chronic toxicity studies with paraquat. Both those studies were inadequate to evaluate the possible effect of paraquat on the central nervous system. Mobley at 53-54. For example, in 1981, ICI's Dr. Litchfield conducted a two-year carcinogenicity feeding study in mice to meet EPA requirements. But the study did not examine paraquat residue in the brain, neuron counts, or neurotransmitter levels, including dopamine. Mobley at 57-58. ICI conducted or commissioned similar long-term feeding studies in laboratory rodents in 1982 and 1983 with similar inadequacies. Mobley at 59-60, 62-63. By this time, ICI and Chevron had accumulated a substantial body of evidence that paraquat could be neurotoxic. In light of this, ICI's and Chevron's failure to examine neurotoxic endpoints can only be viewed as a willful disregard of the potential harm of paraquat.

d. Neurotoxicity tests

Syngenta finally undertook neurotoxicity studies of paraquat in 1996 after studies published by independent laboratories had specifically implicated paraquat in the pathology of Parkinson's disease. WIDDOWSON ET AL. (1996). The Widdowson study observed the brains of rats after a single fatal dose of radiolabeled paraquat and found no neuronal cell death at 24 or 48 hours post-dosing. Mobley at 69-70. A second study administered repeated doses of paraquat over 14 days and observed no loss of neurons. Mobley at 70-71 (citing WIDDOWSON ET AL. (1996b)). The authors observed changes in dopamine levels and movement, but did not attribute them to treatment. Mobley at 70. The second study suffered from conflicting results and both studies were too short to evaluate the neurotoxic potential of paraquat from long-term, chronic exposure. Mobley at 70-71. These studies should have prompted Syngenta to investigate paraquat's long-term neurotoxic potential more thoroughly.

B. Emetics

I have been asked by Plaintiffs' counsel to assume that the following statement is true:

> To keep paraquat products on the market while minimizing the cost of making them less toxic, ICI and Chevron used manipulated scientific data to support the claim that a low concentration of an emetic in paraquat products would prevent deaths caused by paraquat ingestion. These acts likely resulted in the unnecessary deaths of hundreds of people throughout the world.

I have also been asked to assume the authenticity of the documents referenced below and that the accompanying statements in this summary accurately reflect the content of those documents. I have been provided the referenced documents for review.

Imperial Chemical Industries Limited ("ICI") discovered the herbicidal properties of paraquat in 1955,[4] and began selling paraquat herbicide products outside the U.S. in 1962.[5] In 1965, ICI's exclusive U.S. formulator and distributor, California Chemical Company, later known as Chevron Chemical Company ("Chevron"), began selling paraquat herbicide products in the U.S.[6]

Reports of deaths caused by the accidental or suicidal ingestion of paraquat began to appear in medical and scientific journals by no later than 1966,[7] only four years after ICI began selling paraquat products outside the U.S. and a year after Chevron began selling paraquat products in the U.S. By the mid-1970s, with the death toll continuing to rise,[8] ICI and Chevron feared that failure to stem the tide of fatalities caused by paraquat ingestion would lead registration authorities in the U.S. and elsewhere to cancel or refuse to renew paraquat product registrations – that is, to ban the sale and use of paraquat as an herbicide.[9]

In response to this threat to their ability to continue selling paraquat products, ICI and Chevron considered adding (and ultimately did add) three ingredients to their "Gramoxone" (ICI) and "Ortho" (Chevron) paraquat products: (1) a dye, to deter accidental ingestion by giving the product a distinctive color; (2) a "stenching" agent, to deter accidental ingestion by giving the product a foul odor; and (3) an emetic, ostensibly to prevent fatalities by rapidly inducing vomiting following the ingestion of a quantity of the product containing the minimum lethal dose of paraquat.[10]

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[4] Deposition of Syngenta AG and Syngenta Crop Protection LLC (Botham, February 25, 2020) at 48.
[5] Deposition of Syngenta AG and Syngenta Crop Protection LLC (Botham, February 25, 2020) at 97; Deposition of Syngenta AG and Syngenta Crop Protection LLC (Ouzts, June 22, 2020) at 39.
[6] Deposition of Chevron U.S.A. Inc. (Patterson, March 4, 2020) at 60-63, 82; Deposition of Syngenta AG and Syngenta Crop Protection LLC (Ouzts, June 22, 2020) at 34.
[7] SYNG-PQ-01060859 at 877, citing Bullivant, C. M., Accidental poisoning by Paraquat: Report of two cases in man, Br. Med. J. 1, at 1272-73 (1966); Swan, A. A. B., Paraquat poisoning, Br. Med. J. 4, at 551 (1967); Campbell, S., Paraquat poisoning, Clin. Toxicol. 1, at 245-49 (1968); Oreopoulos, D. G., et al., Acute renal failure in case of paraquat poisoning, Br.Med. J. 1, at 749-50 (1968).
[8] *Ibid.* 877-78.
[9] SYNG-PQ-02508147; SYNG-PQ-01843764.
[10] SYNG-PQ-02514781; SYNG-PQ-13098668; SYNG-PQ-03719623; SYNG-PQ-02450023.

The emetic ICI and Chevron ultimately added to their paraquat products was a chemical compound originally designated as "ICI 63197" that ICI's Pharmaceuticals Division had investigated as a bronchodilator,[11] which ICI's Plant Protection Division re-designated as "PP796."[12]

In 1977, Chevron submitted an application to the EPA seeking to exempt PP796 from the requirement of a tolerance when used as an "inert ingredient" in paraquat formulations.[13] Chevron claimed in its application that "Human clinical trials, supported by data from experimental animals, demonstrate that the amount of PP-796 required to induce vomiting in the majority of humans ingesting it is 5 mg (0.08 mg/kg in a 60 kg man).[14]

The EPA ultimately adopted a rule in April 1982 that "exempted [PP796] from the requirement of a tolerance when used as an emetic at not more than 0.1 percent in formulations of paraquat dichloride,"[15] clearing the way for its addition to the paraquat products that by then Chevron was formulating and both Chevron and ICI Americas, Inc. ("ICIA") were distributing and selling in the U.S.[16]

Six weeks after the EPA granted this exemption, the addition of the emetic to paraquat products contributed to the EPA's decision not to include paraquat in a list of products that would be subject to a rebuttable presumption against registration ("RPAR").[17] In fact, as it reiterated in its 1986 paraquat registration standard, the EPA *required* that the emetic be added:

> On April 14, 1982, the Agency established an exemption from the requirement of tolerance for an emetic which is incorporated into paraquat formulations. The emetic is intended to induce rapid vomiting thereby reducing the absorption of paraquat. The Agency is continuing to require the emetic to be incorporated into all formulations of paraquat.[18]

But the EPA was not informed that the data purportedly showing the addition of a mere 0.5 grams of PP796 to a liter of formulated product containing 200-240 grams of paraquat would prevent deaths caused by the ingestion of an otherwise-lethal dose of paraquat by rapidly inducing vomiting had been manipulated by ICI to support that claim. No one other than ICI and Chevron knew this—not the EPA, not other registration authorities, not paraquat buyers or users, not the medical or scientific communities, and not the public. And no one other than ICI and Chevron knew that their own scientists and management either knew or believed the data did not support this claim. No one other than ICI and Chevron knew these facts because ICI and Chevron never disclosed them.

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[11] SYNG-PQ-02450023.
[12] SYNG-PQ-04087247.
[13] SYNG-PQ-01858013 (Volume I); SYNG-PQ-01857812 (Volume II).
[14] SYNG-PQ-01858013 at 8017.
[15] SYNG-PQ-02451086.
[16] CUSA-00099528 at 9529-9530, 9533-9577; CUSA-00075153.
[17] CUSA-00102373 at 2416.
[18] CUSA-00265212 at 5254.

1. Prior to 1976, ICI and Chevron rejected, as ineffective and too costly, adding an emetic to paraquat products to prevent death caused by ingestion of paraquat

ICI first considered adding an emetic to paraquat products at least as early as 1968. Between 1968 and 1974, it repeatedly rejected the idea because, in addition to ever-present concerns about how much this would cost, ICI knew no known emetic—including PP796—would prevent deaths caused by ingestion of a volume of paraquat product containing the minimum lethal dose of paraquat.

In November 1968, Dr. A.A.B. Swan, the head of ICI's Industrial Hygiene Research Laboratory (later known as Central Toxicology Laboratory and CTL) from 1963 to 1978,[19] advised a colleague in the Biological Research department of ICI's plant-protection business that no known emetic would be effective in preventing the absorption of a dangerous amount of paraquat after its ingestion. After explaining that a drug may induce vomiting either by acting on the parts of the central nervous system that trigger vomiting or by irritating nerve endings in the stomach and upper intestine, Swan pointed out that centrally acting emetics "take at least 30 minutes to act because they have to be absorbed from the gut, and there is therefore time for dangerous amounts of paraquat... to be absorbed as well," noting that to be effective, an emetic would have to cause vomiting "within a few minutes."[20]

Two years later, IHRL's Nigel Wright offered a similar response to an inquiry from an ICI overseas subsidiary. After noting that "the question of adding an emetic to paraquat has of course been mooted and gone into in great detail by [Plant Protection] and these laboratories many times in the past," Wright explained that:

> It is unfortunately a fact that no emetic, even the most powerful, would act strongly enough and in time to prevent the absorption of paraquat after swallowing a lethal dose. Paraquat is itself emetic and people who have taken more than just a spoonful have frequently vomited afterwards; this, however, has not always prevented fatal results. You will see, therefore, that it would need first of all a very large quantity of emetic in the formulation, which would make it undesirable from commercial and other points of view, but even if one could find the perfect additive it is most unlikely that it would succeed in preventing fatalities.[21]

In July 1971, A.W. Waitt of ICI Plant Protection's Registration and Technical Literature Section asked Wright to evaluate and give an opinion on the possibility of including as an emetic in paraquat formulations the compound then designated as ICI 63197, attaching a copy of a report on the compound by Dr. G.E. Davies of ICI's Pharmaceuticals Division.[22] In the attached report, Davies had advised Dr. J.M. Winchester at ICI Plant Protection's Jealott's Hill Research Station that "the emetic dose [of ICI 63197] in man is between 4 and 8 mg," and that "it would be necessary to include [a] sufficient [amount] of the compound to ensure that this amount was taken in

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[19] L. Smith, Appreciation of Iain Purchase and Cliff Elcombe, Toxicol. Res., 2018, 7, at 548-49.
[20] SYNG-PQ-02518325.
[21] SYNG-PQ-02517085.
[22] SYNG-PQ-02450188.

whatever volume of paraquat is likely to be toxic."[23] Dr. K. Fletcher responded to Mr. Waitt on behalf of IHRL, explaining that:

> On the question of emetics, we examined this some time ago and turned it down for a variety of reasons; (a) 'Gramoxone' itself is quite a good emetic, (b) there was no really suitable agent to add which would be effective, and (c) the expense would be prohibitive.
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> I believe some of these objections apply to the Pharmaceuticals compound ICI 63,197. I accept it would be effective at a dose of about 10 mg which would imply about 4 g/gallon. Two difficulties I foresee are cost and registration. If you are convinced that the proposition is viable on these two counts, then we would be prepared to evaluate it from the toxicological aspect and try to see if it is effective.[24]

In October 1971, Dr. Fletcher wrote to Dr. P.F.C. Bayliss of the ICI Pharmaceuticals' Clinical Research Department, explaining that "Plant Protection have been casting around trying to find ways of stopping paraquat causing accidental deaths" and asking Bayliss for his views on adding it to commercial paraquat formulations. Bayliss, the author of the report summarizing the results of the human trials ICI Pharmaceuticals had conducted in its attempt to develop ICI 63197 as a drug,[25] responded that for a number of reasons, he believed it was "not suitable for the indication you suggest." Among other things, Bayliss advised Fletcher that ICI 63197 "does not have a clearly defined emetic dose," which he indicated meant a "very high dose" would be required to ensure vomiting in all individuals. He added that because the compound is a centrally acting emetic, even when vomiting does occur, it doesn't happen immediately, but only after enough time for more than a toxic dose of paraquat to have been absorbed.[26] Fletcher responded that he agreed "that the idea of an emetic is probably not of great value,"[27] and informed Waitt that Bayliss "is rather discouraging about [ICI 63197's] use in paraquat formulations."[28]

More than a year later, Dr. Fletcher's assessment of ICI 63197's potential as an emetic in paraquat products remained unchanged. In a November 1972 letter to Dr. D. Seaman of Plant Protection's Jealott's Hill Research Station, with copies to others at Plant Protection, ICI Pharmaceuticals, and IHRL, Dr. Fletcher explained that:

> [C]entrally acting compounds such as... ICI 63197... are effective in low doses (c 10 mg) but are expensive. Also they depend on being absorbed into the general circulation and acting on the brain; they therefore tend to be slow in action, say 15-30 minutes. I have spoken to Dr. Bayliss of Pharmaceuticals Division who agrees that emetics are unlikely to be of help.... I cannot say these compounds will be ineffective but I think that such additions will be very expensive and of marginal use.[29]

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[23] SYNG-PQ-13098675.
[24] SYNG-PQ-02450187.
[25] SYNG-PQ-14420786.
[26] SYNG-PQ-13098673.
[27] SYNG-PQ-02450185.
[28] SYNG-PQ-02450184.
[29] SYNG-PQ-02469717.

In conclusion, Dr. Fletcher said "In general I do not think there is any great future in trying to reduce the toxicity of Gramoxone except by considerable dilution," adding that "We have a considerable amount of sympathy for our position and if we do something sensible, even though it proves not to be very effective, we would be seen to be trying."[30]

Shortly thereafter, on December 14, 1972, Dr. Seaman convened the first meeting of Plant Protection's "Paraquat: Reduction of Hazards by Formulation Project Team." The team recommended that no work be devoted to emetics because, per IHRL, "large quantities are required or they are too slow in action."[31]

On May 16, 1973, Dr. J.T. Braunholtz of ICI Plant Protection met with R.D. Wessel and other Chevron employees at Chevron's offices in Richmond, California. Braunholtz told Chevron that Plant Protection felt an emetic was "not worth pursuing." As to Chevron's position, Wessel wrote that "[Chevron] discussions with [two outside] toxicology consultants confirmed the opinion that further research in this area is probably not warranted," and "The discovery of a practical antidote for treatment of Paraquat poisoning appears to be our best defense for satisfying Paraquat critics, particularly EPA and the Medical Community."[32]

The pressure on ICI and Chevron to solve the problem of fatalities caused by the ingestion of paraquat continued into 1974. At a meeting on February 27, 1974 in Richmond, California, Dr. A. Calderbank of ICI Plant Protection, R.D. Cavalli, a toxicologist with Chevron Environmental Health Center, Dr. J.N. Ospenson, Chevron's Manager of R&D, and representatives of Chevron's Registration Section and Market Development function discussed the problem and potential responses to it.[33] The notes of this meeting, which were widely circulated within ICI,[34] did not mention any discussion of adding an emetic to paraquat products.

Four months after this meeting, on June 20, 1974, Dr. Fletcher again explained to a colleague, this time at ICI's Australian subsidiary, why adding an emetic to Gramoxone would not be effective:

> The suggestion of putting an emetic in Gramoxone has been looked at and the drawback is mainly one of cost and compatibility. I estimate a fatal dose as 10 ml of the 20% formulation and, therefore, the emetic dose must be contained in this or a lesser volume. Can you estimate the cost of putting 500 emetic doses of ipecacuanha in each gallon of Gramoxone? If you try to use a metal, such as copper or antimony, the required strength is about 10% and is both too costly and incompatible with the paraquat. One requires an immediate emetic effect and this rather rules out the centrally acting compounds such as apomorphine, even if these should be required in small doses and the cost could be kept down.[35]

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[30] *Ibid.* at 9718.
[31] SYNG-PQ-02491713 at 1714-15.
[32] CUSA-00046646 at 6656-657.
[33] SYNG-PQ-02508147.
[34] *Ibid.* at 8150.
[35] SYNG-PQ-02514408.

In the Winter/Spring of 1974, ICI and Chevron had some concern that the EPA might cancel paraquat registrations because of fatalities caused by accidental ingestion.[36] In October of that year, the EPA promulgated its RPAR regulation.[37]

In December 1975, ICI reported to Chevron that during a late November visit to ICI's Plant Protection Division in the U.K., the Director of the Registration Division of the EPA's Office of Pesticide Programs had told ICI that Ortho Paraquat CL, Chevron's U.S. paraquat product, had been placed on the EPA's list of products subject to a rebuttable presumption against registration ("RPAR"); although this turned out to be incorrect, the possibility that the EPA would cancel or deny re-registration outside the RPAR process continued to exist.[38]

As 1975 drew to a close, the possibility of adding an emetic to paraquat products was raised again. On December 23, 1975, Dr. Winchester—who, as noted above, had known about ICI 63197 since 1971—wrote to Dr. Swan, suggesting it would be well worth a substantial monetary investment of several hundred thousand British pounds to embark on a research project "to discover and synthesise [sic] new chemical compounds which may be much stronger emetics than those we know of today."[39]

2. In 1976-1997, based on ICI human trials data that allegedly support an estimate of 5mg as the effective emetic dose of pp796 in man, ICI and Chevron decided to use pp796 as an emetic and seek approval to do so.

Dr. Swan responded to Dr. Winchester on January 5, 1976. Instead of approving the launch of a research program to attempt to discover and synthesize new compounds for potential use as emetics in paraquat products, Dr. Swan said he was appointing a team led by Dr. Michael Rose to explore the feasibility of doing research along those lines.[40]

In his memo scheduling the initial, January 29, 1976 meeting of this team, Dr. Rose pointed out that "Paraquat poisoning is causing the Company considerable concern, particularly since the Environmental Protection Agency in the USA is currently questioning the safety of the product." In the same memo, Dr. Rose set "within an hour" as the standard for how quickly vomiting would have to be induced to make preventing the absorption of a lethal quantity of paraquat possible, but did not explain the scientific basis for this standard (which was much longer than the "few minutes" or less than 15 minutes that Drs. Swan and Fletcher had previously explained was the time within which an emetic would have to induce vomiting).[41]

Before the initial meeting of the working team, Dr. Foulkes wrote to Dr. Rose on January 26, 1976, setting forth the Plant Protection Division's view of the criteria it would apply to an emetic for use in Gramoxone. Although he acknowledged this was an "ideal view," he made clear that PPD "would not imagine using a compound far removed from such criteria." Among the criteria were that the emetic be effective in a lethal volume of Gramoxone and that it be "an established

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[36] SYNG-PQ-01843764 at 3764-65.
[37] *Ibid.* at 3765.
[38] *Ibid.* at 3764.
[39] SYNG-PQ-03719628.
[40] SYNG-PQ-02450112.
[41] SYNG-PQ-03719624.

emetic agent, obviating the need for extensive toxicological testing,"[42] a criterion that effectively ruled out any project to discover and synthesize new emetic compounds for use in paraquat products.

On February 9, 1976, Dr. Rose issued a report of the working party dated January 29, 1976, the date of the initial meeting.[43] The working party considered only existing emetics, one of which was which was ICI 63197. The report described ICI 63197 as "a potent, centrally acting emetic, causing vomiting in man with oral doses on the order of 5mg,"[44] but did not provide a source for this information or explain how the specified dose was determined or estimated (as noted above, the emetic dose had previously been reported by the ICI Pharmaceuticals Division to be between 4 and 8mg and by Dr. Fletcher to be about 10mg, and Dr. Bayliss, who reported on the ICI Pharmaceuticals Division human trials, had stated there was no clearly defined emetic dose).

In a March 23, 1976 memo, to a dozen ICI scientists and managers, D.M. Foulkes reported the results of a meeting held the day before to establish a program for the evaluation of ICI 63197 (now designated R.50796) as an emetic to be added to paraquat, with the objective of obtaining clearance for its use in 1977. The memo asserted without elaboration that "from existing human data a concentration of 0.5g/litre is likely to produce emesis upon ingestion of 10ml of Gramoxone."[45] The only "human data" that existed then, or ever, was the data from the ICI Pharmaceuticals Division's human trials of ICI 63197.[46]

An October 6, 1976 ICI report entitled "An Emetic Formulation of Gramoxone" noted that a growing number of accidental deaths had "led to pressure on ICI and its agents overseas by registration authorities," particularly in Western Europe. The report stated that while the addition of an emetic had previously been considered of little value, "a compound has now been discovered" that "will produc[e] rapid and effective vomiting in man at low concentrations," which "it is believed... will greatly reduce the risk of death following the ingestion of paraquat."[47] As to how the compound would perform in Gramoxone, the report said:

> The level of inclusion of PP796 in 'Gramoxone' has, after careful consideration of human data, been established as 0.05% w.v., i.e. 5 mg in 10ml of 'Gramoxone'. This is confidentially expected to produce vomiting within 15 minutes in 75-85% of those ingesting such a quantity, which is the approximate minimum lethal dose of 'Gramoxone' in man.[48]

The report did not explain either how the stated concentration of PP796 in Gramoxone had been determined or the source of the expectation that this concentration would produce vomiting within 15 minutes in 75-85% of those ingesting 10ml of Gramoxone.

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[42] SYNG-PQ-03719623.
[43] SYNG-PQ-02450023.
[44] *Ibid.* at 0023-24.
[45] SYNG-PQ-02450073.
[46] Deposition of Syngenta AG and Syngenta Crop Protection LLC (Botham, June 19, 2020) at 1268.
[47] SYNG-PQ-02450673.
[48] *Ibid.* at 0674.

On October 4, 1976, Chevron had held an internal meeting about paraquat formulations. According to the minutes of that meeting:

> Cavalli reviewed the toxicology data on PP-796, which was given to him on the day of his departure from the U.K. following the liaison meetings the first week in September. The data do not support PPD's contention that 5 mg of PP-796 in 10 ml of formulated product will produce emesis within 15 minutes in 80% of those ingesting such a quantity. The animal and human data made available by PPD would indicate that PP-796 would have to be administered at 2-5 mg/kg and even then the rate of individuals responding and the time to response is such that the survival rate of ingestion cases may not be significantly improved. There are serious discrepancies between the actual data provided and what PPD has been telling us verbally.[49]

Dr. Cavalli explained his analysis of the data that led to these conclusions in a Chevron internal memo dated October 13, 1976.[50] He noted that the only information Chevron had about human experience with PP796 was the 1973 report by Bayliss on the results of the ICI Pharmaceuticals Division's human trials of ICI 63197, which ICI had confirmed was the only documentation of the compound's emetic action in humans.[51] After summarizing the data on emesis from each of the human trials, Dr. Cavalli stated "As you can see, these data do not support the statement made in Braunholtz's letter and confirmed in Slade's telex. As far as I can tell, no one has vomited within 15 minutes."[52] Dr. Cavalli also observed that the 5mg in 10ml dose ICI was proposing to use in paraquat formulations would be about 0.06mg/kg for a 170-pound man, "significantly lower than the 2-3 mg/kg found effective in the dog and monkey," and although he had been told at CTL that the compound was more active in humans, "the data does not support this."[53]

In October 1976, the ICI Executive Directors' Committee was presented with a report authored by P. Slade and entitled "Emetic Formulation of Paraquat: Proposed Strategy for Introduction Worldwide," EDC Paper No. 729.[54] The EDC paper recommended actions to be taken to implement a strategy for introducing the emetic formulation containing PP796 and discussed various topics related to that strategy.

In discussing the technical case for adding PP796 to Gramoxone,[55] the EDC paper stated "PP796 seems to have all of the properties needed in an emetic agent to be added to paraquat formulations," including "That it will produce rapid and effective vomiting in man at low concentrations

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[49] CUSA-00256176 at 6363-6364.
[50] CUSA-00305753.
[51] *Ibid.*
[52] *Ibid.* at 5754.
[53] *Ibid.*
[54] SYNG-PQ-04262278 at 2668-2695.
[55] Other topics discussed in the EDC report included patent status and strategy (both PP796 and paraquat formulations incorporating it were or were to be patented); registration strategy (attempt to convince registration authorities to prohibit non-emeticized paraquat formulations, noting the belief that the prospects of competitors discovering suitable alternative emetics were very remote); proposed timetable for introduction; production plans and price; and publicity. *Ibid.* at 2674-85.

and with no adverse side effects. It is believed that this will greatly reduce the risk of death following ingestion of paraquat."[56] The paper acknowledged the importance of adding the emetic at the right concentration, and indicated the concentration selected was 0.05% w.v., or 5 mg in 10ml of Gramoxone, and stated this "is expected to produce vomiting within 1 hour in the majority of those ingesting such a quantity, which is the approximate minimum lethal dose of Gramoxone in man."[57]

As evidence for this rate of addition, the EDC paper cited Appendix 1, an October 18, 1976 draft report by Dr. Rose (with handwritten note "see CTL/390, 1976"),[58] which stated in relevant part "From the limited data available in man, therefore, it can be argued that a dose of 5 mg should certainly cause nausea and ought to induce vomiting in approximately 70% of those ingesting it (Table 1)," with the words "approximately 70%" struck through and "the majority" handwritten above them; the same handwritten change appears in the report's summary.[59]

On October 19, 1976, D.M. Foulkes of ICI wrote to Dr. Nils Ospenson of Chevron, enclosing a draft report by Dr. Rose, Report No. CTL/R/[390].[60] On the subject of the emetic dose of PP796 in man, the draft report claimed that "at a level of 5 mg in 10 ml (0.05%)," "[i]t is estimated that about 70% of those ingesting 10 ml of this formulation will vomit within an hour,"[61] the same claim made (before the handwritten changes) in the draft attached as Appendix 1 to the EDC report.

In an October 21, 1976 telex from Chevron's Dr. Cavalli to Dr. Rose, with copies to several others at ICI, Dr. Cavalli said he had reviewed the studies provided by ICI and was "concerned as argument for 5mg being an effective emetic dose in man is weak and still does not support the statement that [it] will cause emesis in 85 percent by 15 minutes." He told ICI he believed "EPA will likely require actual data regarding effectiveness of dose recommended in humans," and suggested a volunteer human trial to evaluate the dose-response relationship for the emetic.[62]

When Dr. Rose responded to Dr. Cavalli on October 26, 1976, he admitted that the "clinical data on [PP]796 is certainly weak," said a volunteer study was not feasible for ethical reasons, and told Dr. Cavalli that "In the absence of hard evidence, I have produced a draft report making the case for addition at 5mg in 10ml," and that "We believe this case adequate for proposed European registration."[63]

On November 2, 1976, Dr. Rose sent Dr. Cavalli a copy of the final version of CTL/R/390.[64] It was largely identical to the drafts described above, but claimed the emetic would be expected to produce vomiting within 1 hour in the majority of those ingesting such a quantity, reflecting the handwritten change made to the copy attached as Appendix 1 to the EDC report. The final report does not explain either this change or the discrepancies between the draft and final versions of

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[56] *Ibid.* at 2671.
[57] *Ibid.* at 2671-72.
[58] *Ibid.* at 2686-93.
[59] *Ibid.* at 2689, 2686.
[60] CUSA-00088288 at 8442-8451.
[61] *Ibid.* at 8444.
[62] CUSA-00088288 at 8433.
[63] CUSA-00305732.
[64] CUSA-00088288 at 8398.

CTL/R/390 and the October 6, 1975 report "An Emetic Formulation of Gramoxone" discussed above ("expected to produce vomiting within 15 minutes in 75-85%").

On November 11, 1976, Dr. Cavalli wrote to Dr. Rose, stated that although he had advised Nils [Ospenson] that "the last arguments will be sufficient to send to the EPA with our first submission..., I do feel that they may well request further work and that demonstration of the dose/effect relationship of PP 796 as an emetic in man be asked for."[65]

In November 1976, the ICI Plant Protection Division's Development Project Team issued a report entitled Paraquat: Reduction of Hazard,[66] which in relevant part consisted largely of information contained in documents discussed above. The report included the following appendices:

- Appendix I - Rose, CTL/R/390, The Concentration of PP796 Required to Produce Emesis in Experimental Animals and An Estimation of the Emetic Dose in Man[67]
- Appendix II – Rose et al., CTL/R/391, The Effect of Administration of an Emetic (PP796) on Paraquat Toxicity in Dog and Monkey[68]
- Appendix III – tables of data on paraquat fatalities and recoveries from 1964 to 1976 for the UK and the World including the UK, data on paraquat fatal accidents between April 14 and October 1, 1976[69]

As noted in my Introduction, on April 1, 1976, Chevron submitted an application to the EPA seeking to exempt PP796 from the requirement of a tolerance when used as an "inert ingredient" in paraquat formulations. Included in this application were ICI Pharmaceuticals Division's toxicology and clinical trial reports regarding ICI 63197, Dr. Rose's report CTL/R/390, and 17 other ICI reports.[70]

3. 1979-1986: EPA grants tolerance for and requires emetic; Lewis Smith recommends increasing concentration of emetic, recognizes that emetic doesn't reduce mortality at current concentration

Chevron's application was still pending when, in a December 21, 1979 letter, Dr. Calderbank advised Dr. Rose that publication of some of the emetic work "might draw attention to the emetic and cause authorities or individuals to seek confirmation or reassurance that the emetic really does work in the human poisoning situation." Dr. Calderbank explained the potential consequences: "our inability to provide this confirmation might prejudice the exclusive position we are trying to build up with authorities opposite competitive [paraquat]." In closing, Dr. Calderbank stated "we should await good evidence of the efficacy of the emetic in the human situation before publication of the CTL work."[71]

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[65] SYNG-PQ-02515610.
[66] SYNG-PQT-ATR-14192407.
[67] *Ibid.* at 2440.
[68] *Ibid.* at 2448.
[69] *Ibid.* at 2461-63.
[70] SYNG-PQ-01858013 at 8120-21.
[71] SYNG-PQ-03719852.

"Emetic Policy" was one of the subjects of a September 17, 1980 ICI Plant Protection Division report presented at a September 24, 1980 Board Meeting.[72] The report related the history of emetic policy: initially, to register and introduce the emeticized product in all markets, seeking to convince registration authorities to require an effective emetic in all paraquat formulations; subsequently, to register and introduce the emeticized product in all markets that wanted it, even if registration authorities could not be convinced to exclude non-emeticized paraquat products.[73]

The report notes that attempts had been made for two years to obtain evidence of the efficacy of the emetic from human poisoning cases, but concludes "it is unlikely that statistical evidence, showing that the emetic has caused a reduction in the total number of deaths from paraquat poisoning, will be obtained...."[74]

An August 21, 1981 ICI "Company Secret" paper titled "Emetic Paraquat: USA"[75] explained that the position ICI must now take on the effectiveness of the emetic formulation "comes down to a belief that it may contribute to saving a small number of lives, all of them of people who have swallowed small amounts of paraquat," but acknowledged that "There are already some in the toxicological field outside ICI who consider that the emetic is ineffective in saving life" and that "it may be difficult, perhaps impossible, for us to produce evidence to the contrary."[76]

As to how ICI's views on the efficacy of the emetic should affect general policy on emetic introductions, the paper stated: "In the light of the current view of the probably small toxicological benefit which arises from inclusion of the emetic in paraquat, it is difficult to see how a case can now be made to registration authorities that an emetic should be included in all paraquat products, which is the means by which a commercial benefit is obtained from the emetic."[77]

ICI's views on the efficacy of the emetic led to the conclusion that its introduction in the U.S. should be delayed:

> The most prudent course of action therefore seems to be to delay introduction of PP796 in the USA until our views on its efficacy and the possibility of the EPA giving us an exclusive position are further clarified; by this time PP796 may no longer be giving us an exclusive position in several markets, in which case we need not fear difficulties in those markets because of non-introduction of emetic in the USA. A year's delay is suggested: such a delay can be explained to the outside world by reference to "production difficulties."

As noted in the Introduction, in April 1982 the EPA adopted a rule exempting PP796 from the requirement of a tolerance when used as an emetic in paraquat products. The exemption had two restrictions: "this ingredient may not be advertised as an emetic" and "the paraquat product may not be promoted in any way because of the inclusion of this inert ingredient."[78] But these re-

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[72] SYNG-PQ-02451102.
[73] *Ibid.* at 1103.
[74] *Ibid.* at 1104-05.
[75] SYNG-PQ-02451088.
[76] *Ibid.* at 1088-89.
[77] *Ibid.* at 1089.
[78] SYNG-PQ-02451086.

strictions did not deter ICIA from advertising PP796 as an emetic and using it to promote its paraquat product: in marketing its new "Gramoxone Super" paraquat product, ICIA represented to potential customers and users that "In the unlikely event of swallowing, the emetic in GRAMOXONE SUPER will induce vomiting."[79]

On October 10, 1984, Dr. Lewis Smith at CTL wrote to T.B. Hart at ICI's Plant Protection Division in response to a report by Hart on the efficacy of PP796 in reducing fatalities due to paraquat. Dr. Smith advised Hart that "Apart from considerations of cost, safety to user, environmental issues etc., it strikes me that what we need is a potent emetic which causes vomiting within 5 minutes of swallowing a potentially lethal dose of paraquat. PP796 does not meet this criteria." He acknowledged that PPD had previously considered the possibility of increasing the amount of PP796 in paraquat formulations in order to improve the emetic response and had decided against this, but suggested a test in one market. In closing, Dr. Smith explained that "From the available knowledge we have of paraquat poisoning I am confident that early emesis (within 10 minutes) would reduce the toxicity of paraquat formulations."[80]

In the years that followed, the recommendation to increase the concentration of the emetic was made repeatedly. In addition, echoing the concerns Dr. Cavalli raised in 1976, questions were raised within ICI itself about the integrity of the scientific analysis that had led to the concentration that had been deemed sufficient at that time.

For example, Notes of the First Meeting of Paraquat Strategic Action Committee held at Fernhurst on November 22, 1985, Section 6, Increased Emetic Concentration (Report of Sub-Group), record that CTL believed a five-to-tenfold increase in the emetic concentration in Gramoxone could improve the survival rate from paraquat poisonings in man significantly.[81]

4. 1987-2000: CTL'S DR. John Heylings repeatedly recommends increasing concentration of emetic and Dr. Smith agrees, but no change is made

In a January 19, 1990 memo from Dr. Jon Heylings to Dr. Lewis Smith on the subject Emetic Concentration in Paraquat Formulations,[82] Dr. Heylings said he had he reviewed the reports on PP796/ICI 63197 produced by ICI Pharmaceuticals and CTL from 1970 through 1986, including the 1976 report by Dr. Rose, CTL/R/390, and pointed out that "[s]tudies of poisoning cases involving emeticised paraquat formulations have not provided any definitive evidence that the introduction of 0.05% PP796 to paraquat concentrate in 1979 has resulted in a significant reduction in the number of fatalities attributed to the herbicide."[83]

According to Dr. Heylings, he was "not entirely surprised" to learn this, because "My conclusion from studying the scientific evidence from clinical studies with the emetic is that the concentration of PP796 recommended in 1976 is probably well below an effective emetic dose in man," explaining that conclusion in some detail,[84] including: (1) the significance of the animal studies,

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[79] SYNG-PQ-01832461 at 2463.
[80] SYNG-PQ-03719874.
[81] SYNG-PQ-02494068 at 4071-72.
[82] SYNG-PQ-26134258 at 4258-4265.
[83] *Ibid.* at 4258.
[84] *Ibid.*

including a consistency in the effective emetic dose suggesting little or no species differences in the response to PP796; (2) the insufficiency of the data from the clinical studies to support a scientifically valid conclusion that man was more sensitive than other species to the emetic; and (3) the absence of any physiological reason why man should be more sensitive to emesis.[85]

In conclusion, Dr. Heylings said his "personal viewpoint, based on scientific judgment of available toxicological data together with the extensive clinical poisoning data, [was] that the concentration of PP796 should be increased by ten-fold, from 0.05% to 0.5%," reducing the ratio of paraquat to emetic from 400:1 to 40:1.[86]

PPD's Dr. Jaggers responded on January 25, 1990, that he was surprised by the limited data on the emetic effects of PP796 in man. Dr. Jaggers asked whether Dr. Heylings was sure the Pharmaceuticals Business didn't have more data, but didn't express any disagreement with Dr. Heylings' analysis or conclusions.[87]

Dr. Heylings responded on January 31, 1990. He assured Dr. Jaggers he had studied all of the evidence that existed at ICI Pharmaceuticals, and provided both a summary and details, taken from the 1973 Bayliss report, of the results of the ICI Pharmaceuticals volunteer study and subsequent clinical trials, along with calculations of the percentage incidences of vomiting "per dose" and "per person." In closing, he reported that he had discussed this data and the historical aspects of the emetic in paraquat formulations with Dr. Smith, who had agreed to arrange a meeting to revisit this issue.[88]

Although it doesn't directly address the appropriate concentration of the emetic, a report by Dr. Heylings and Dr. Smith dated February 19, 1990, "Toxicology of Multiple Emulsion Formulations of Paraquat,"[89] provides information that assists in understanding the factors at play. In particular, the report indicates that:

- "Paraquat is absorbed rapidly but incompletely from the gastrointestinal tract following oral ingestion in man;"
- "GRAMOXONE contains an emetic (PP796) which, if a sufficient dose is given, will induce vomiting;"
- "Since the emetic itself has to be absorbed there is a latency between oral ingesting and emesis;" and
- "Furthermore, since GRAMOXONE is a free-flowing liquid, it empties from the stomach into the small intestine (the site of paraquat absorption) within a few minutes which makes it more difficult to remove by emesis."[90]

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[85] *Ibid.*
[86] *Ibid.* at 4259.
[87] SYNG-PQ-26134258 at 4266.
[88] SYNG-PQ-26134258 at 4267-4268.
[89] SYNG-PQ-03709681 at 9742-9762.
[90] *Ibid.* at 9751.

On February 28, 1990, ICI Agrochemicals issued a report titled "Safer Paraquat Formulations,"[91] which detailed the progress made by the Safer Paraquat Formulations Project. One of the recommendations the report made was to "Consider the case for raising the level of emetic in current 'Gramoxone' formulations to improve safety margins."[92] Elaborating, the report stated "It has been found that increasing the concentration of the emetic in 'Gramoxone' by a factor of 5 resulted in a minimum of a 2-3 fold safety factor over standard 'Gramoxone.'"[93]

The report also discussed the results from 5 years of monitoring poisoning cases after PP796 was added to paraquat formulations, stating "There was no definitive evidence from this large database that inclusion of the emetic had resulted in a reduction in oral toxicity of paraquat."[94] It acknowledged that "the original decision to add 0.05% emetic to GRAMOXONE was probably an underestimate of the effective emetic dose in man," noting that "The time-to-vomit parameter is extremely critical to remove non-absorbed paraquat. Recent studies suggest that animals must remove the herbicide within 20 minutes of ingestion in order to survive a lethal dose of paraquat. In order to achieve this, available data suggests that the minimum concentration of emetic in GRAMOXONE should be some 5 times higher than currently used."[95]

Under the heading "Strategy," the report discusses the pros and cons, from product safety and business perspectives, of a proactive approach of promoting a safer formulation in all markets versus a reactive approach of keeping safer formulations "on the shelf" to provide a "fall-back option" if and when existing product registrations are threatened, and indicates ICI opted for the reactive approach: to offer a safer paraquat formulation only if and when registration authorities make doing so the only way to keep selling paraquat. [96]

In a September 5, 1990 memo to Dr. Smith, Dr. Heylings again raised the issue of the human data on the PP796.[97] Having reviewed the data on ICI 63197 in the 1970 Farrell and 1973 Bayliss ICI Pharmaceuticals reports and noting that "It was clearly crucial that PP796 must be added to Gramoxone at an effective concentration in a minimally lethal dose of Paraquat," Dr. Heylings pointed out the human data presented in Dr. Rose's report, CTL/R/390R, was very misleading, and attached a table comparing the data from that report to the original data from the Bayliss report.

Dr. Heylings identifies what he calls "three important differences" between the data from CLT/R/390R, Dr. Rose's Report, and PH20992C, Dr. Bayliss's report on the clinical trials: (1) that Dr. Rose omitted data from 2 volunteers who were dosed with 3mg of PP796; (2) that data showing a 4/37 vomit response from patients with various diseases at 2mg PP796 has replaced a 0/3 response in the volunteer study on which the rest of the data is based; and (3) that Dr. Rose counted as an incident of vomiting a patient who vomited at 2 hours after receiving

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[91] SYNG-PQ-02639780.
[92] *Ibid.* at 9783.
[93] *Ibid.* at 9785.
[94] *Ibid.* at 9788-89.
[95] *Ibid.* at 9799.
[96] *Id.* at 9811-12
[97] SYNG-PQ-26134258 at 4270-4272.

8mg PP796, the highest dose anyone in the clinical trials received, despite the fact that Dr. Rose himself stressed the importance of vomiting occurring within 30 minutes.[98]

Dr. Heylings pointed out that Dr. Rose produced a "plausible dose-response relationship" by normalizing "selected data."[99] He explained that "on examination of the full data there is no such dose response," and that "The minimal effects observed at 4 and 8mg PP796 suggest that 4-8mg doses are probably nearer threshold in man not maximal."[100]

In closing, Dr. Heylings emphasized the importance of what he had found in investigating the basis for Dr. Rose's determination of the concentration of PP796 to be included in Gramoxone:

> I have documented my findings in this letter since I feel that this issue is extremely important in the impending ICI Agrochemicals Board Paper which is to discuss increasing the level of emetic in Gramoxone. I am fully aware that a 5 fold increase in emetic concentration was recommended in 1985. This followed further observations in the dog with Paraquat and PP796. Our current studies in 1990 are in very close agreement. Thus, the effective dose of PP796 in dogs to produce emesis within 30 minutes is about 0.2mg/kg. Therefore, if man were to respond to the emetic at similar dose levels as the dog, then a minimal lethal dose of Gramoxone (10ml) should contain at least 15mg PP796 or three times the 1976 proposed level.
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> The whole argument is based on whether or not there are species differences in response to PP796. I think it is extremely unlikely that PP796 is ten times more potent in man compared to pig, monkey and dog as stated by Rose, having reviewed all the data at my disposal.[101]

On October 11, 1990 Dr. Smith responded to Dr. Heylings and assured him that in his capacity as Paraquat Project Manager, he would "ensure that this matter is raised with the Business."[102]

Dr. Smith wrote to Dr. Heylings on this subject again on November 6, 1990.[103] Contrary to statements by several others in documents discussed above dating from 1968-1972, Dr. Smith suggested that in 1976, when the concentration of the emetic was set, "If my memory serves me correctly it was not even partly appreciated that the time to emesis in man that is required to prevent the absorption of paraquat is less than 30 minutes."[104] He explained that "I, and others at CTL, came to the view some years ago that it would be useful to increase the concentration of emetic in paraquat formulations. This view was arrived at on the basis on our experience of human poisoning and some experimental data generated in dogs."[105]

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[98] *Ibid.* at 4270.
[99] *Ibid.* at 4271.
[100] *Ibid.*
[101] *Ibid.*
[102] SYNG-PQ-26134258 at 4269.
[103] SYNG-PQ-26134258 at 4273-4274.
[104] *Ibid.* at 4273.
[105] *Ibid.*

However, Dr. Smith agreed with Dr. Heylings on the ultimate conclusion: "it appears that there is no disagreement between us that an increase in emetic of 3-5 fold ought to be evaluated."[106] The last paragraph of Dr. Smith's letter suggests his only point of disagreement with Dr. Heylings was about whether to let sleeping dogs lie: "In conclusion I do not intend to pursue any further the reasons for the inclusion of PP796 at 0.05% as decided in the early part of 1976."[107]

Neither ICI nor Zeneca ever increased the concentration of PP796 in Gramoxone. However, it obviously was feasible to do so, because according to an October 26, 1990 memo from Dr. Heylings to Dr. Smith, ICI did increase it, by a factor of three, while at the same time reducing the concentration of paraquat in the product by half, in the formulation it sold in France, resulting in an overall six-fold increase in the ratio of emetic to paraquat and a significant reduction in toxicity.[108]

On April 9, 1991, a little more than 14 months after explaining to Dr. Jaggers what the ICI Pharmaceuticals clinical trial data showed about the efficacy of the emetic, Dr. Heylings raised the issue with him again, this time enclosing background data on the emetic issue, including correspondence, the original ICI Agrochemicals strategy document that included the Rose report, and the Bayliss report on the clinical trials. He noted that the two of them had discussed that the data presented in the Rose and Bayliss reports differ markedly, and in closing, stated closed "I feel that the combination of current animal data with the emetic, together with the information I have brought to your attention, would convince the Business to sanction the cost of the emetic plant prior to the estimated date of 1993."[109]

In response, on April 26, 1991, Dr. Jaggers, the Regulatory Toxicology Manager for paraquat, appointed a team, led by a Dr. Oliver and including Dr. Heylings and Dr. R.C. Scott, the Paraquat Product Manager, to address whether, as Dr. Heylings had said, a stronger argument for increasing the emetic could be made based on a new review of the data.[110] On the same day, Dr. Jaggers wrote separately to Dr. Heylings emphasizing his view that the review should be "positive" and forward-looking; in other words, should let sleeping dogs lie.[111]

On June 12, 1991 Dr. Heylings sent a memo to G.A. Willis, N.N. Sabapathy, and others on the subject of Paraquat Human Data, in which he summarized data on paraquat human poisonings that he had obtained from various internal and external publications.[112] Dr. Heylings presented data from 9 studies of paraquat poisonings in four countries—the UK, France, Germany, and Japan—over various periods from 1972 to 1988, with the combined data showing 490 deaths from 647 cases, a 76% mortality rate.[113] Dr. Heylings explained in some detail that by increasing the concentration of the emetic, many of these deaths could have been avoided.[114]

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[106] *Ibid.* at 4274.
[107] *Ibid.*
[108] SYNG-PQ-03709681 at 9695-9697.
[109] SYNG-PQ-26134258 at 4275.
[110] SYNG-PQ-26134258 at 4276-4277.
[111] SYNG-PQ-26134258 at 4278.
[112] SYNG-PQ-03709681 at 9698-9705.
[113] *Ibid.* at 9701.
[114] *Ibid.* at 9699-9700.

More than nine years later, on September 28, 2000, nothing had changed. In an email to Emma Ashford on that date, Dr. Heylings explained that:

> Assuming a 70kg man an effective dose is 70x0.5=35mg PP796 in a lethal dose of Gramoxone which is widely agreed to be 15ml. This indicates that a concentration of 2.3mg/ml PP796 would cause vomiting within 30min in a minimally lethal dose of Gramoxone. We currently put 0.5mg/ml in the product. The 2.3mg/ml emetic version of Gramoxone provided a 5-fold safety factor in the dog (CTL/R/1250). Based on the similarities in dose response curves of the 5 vomiting species studied I would expect this to give a 5X safening in man.[115]

C. Syngenta recognizes the "threat" the literature poses to paraquat sales

Syngenta's uncertainty campaign regarding the connection between exposure to paraquat and Parkinson's disease follows the template instituted by Big Tobacco and perfected over the years by many industries. Remarkably much of the very template is laid out in internal Syngenta documents.

1. Syngenta's "influencing and publication strategy"

Internally, Syngenta was blunt about its intent. By 2001, it had formed a "Paraquat/Parkinson's Disease Task Team" to report to its Paraquat Steering Group (chaired by Dr. Lewis Smith). Updates were also to be provided to the PLT (later known as the PILT (Paraquat Issues Leadership Team)). The team met at Syngenta's Central Toxicology Laboratory (CTL) in England. Syngenta pursued a "science-based" "influencing strategy" to influence (unabashedly, at least internally) outside scientific research. A "techno-regulatory team" was also proposed, along with a "Proposal for Influencing Strategy" in which the "techno-regulatory team" would "identify the threats to paraquat from the [Parkinson's Disease] hazard models."

In the early 2000s, Syngenta created a Paraquat/Parkinson's Disease Task Team. At an October 2001 meeting, the team came up with a "Proposal for Influencing Strategy," a purportedly "science-based approach to an influencing strategy" intended "to influence academia, and regulatory and NGO 'environments.'"[116] The objective was very clear: defend paraquat from the threats posed by independent science and regulation. Syngenta would set up a "techno-regulatory team" that would "identify the threats to paraquat from the PD hazard models" in order to "maintain and safeguard paraquat registrations." For the next fifteen years at least, Syngenta personnel, including attorneys and scientists, along with outside product defense scientists hired to defend paraquat, continued to apply this strategy. In their internal deliberations, they considered any research that linked paraquat with PD as a "threat" that needed to be countered in order to ensure that government agencies would not limit paraquat sales. They funded studies and made presentations that tried to convince academic scientists and regulators that paraquat did not increase PD risk, using many of the same tactics described at the beginning of this report. [117]

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[115] SYNG-PQ-21802228.

[116] SYNG-PQ-00479279 at 9283.

[117] For additional examples of internal documents of the kind discussed in this section of the report, *see* Appendix A, which includes additional examples of documents making clear that the results of any study that show a link between paraquat and PD would have to be challenged.

Starting as early as 2002, Syngenta hired product defense scientists who participated in strategy sessions on these topics, and then wrote papers reviewing evidence (not creating new science) that reached conclusions supportive of Syngenta's goals, without disclosing their employment by Syngenta. For example, in April 2002, Colin Berry signed a consulting agreement with Syngenta.[118] Dr. Berry was a member of Syngenta's "Extended Health Science Team," attending meetings in 2009[119] and then serving as the first author of a review paper "Paraquat and Parkinson's Disease," which fulfilled the objectives of the strategy. It concluded that "the epidemiological and clinical evidence that PQ may favour the onset of PD is inconclusive." [120] It disparaged the toxicological studies linking paraquat with PD, concluding that the "experimental [animal] studies that might inform us do not reflect human exposure."[121] These were just the results needed by Syngenta. The authors of the paper were paid by Syngenta, and there are numerous emails documenting Syngenta's comments and editing of the paper.[122] However, the paper's conflict of interest disclosure did not mention Syngenta, and only noted the authors "have worked with pharmaceutical and chemical companies and external advisors."[123]

It appears from the emails that the purpose of this study was to defeat the threat of regulation and shape the scientific understanding of paraquat, not produce objective scientific evidence. For example, in SYNG-PQ-22035417 the Syngenta team reviewed draft papers and discussed how different audiences (including regulators) might read the studies that Syngenta had commissioned, and how Syngenta might use them "in regard to supporting response to regulatory authority or other external questions." This discussion is continued in SYNG-PQ-20736297.

Similarly, several of Syngenta's consultants, along with two Syngenta scientists published a paper entitled "Toxicology and Epidemiology: Improving the Science with a Framework for Combining Toxicological and Epidemiological Evidence to Establish Causal Inference,"[124] which details an extensive process of evidence review necessary to reach a conclusion about a causal relationship involving a toxic exposure and disease. Following this process would make it difficult to prove the causal relationship between paraquat and PD. Notably, the example given for a model of this type of investigation is one that was used by a Syngenta consultant to exonerate atrazine, another controversial pesticide manufactured by Syngenta, in the causation of breast cancer. There is no mention in the article that at least three of the academic authors were Syngenta consultants.

In 2004, scientists employed by Exponent, a leading product defense firm, were conducting an "Evaluation of the Epidemiologic and Animal Data Associating Pesticides with Parkinson's Disease." This review was first presented as a poster at a scientific meeting and then published in a scientific journal[125] and was commissioned by CropLife America, the trade association representing pesticide producers. There are several memos between Abby Li, the first author and an

[118] SYNG-PQ-02322111.
[119] SYNG-PQ-04982646, SYNG-PQ-19644599.
[120] SYNG-PQ-37237312 at 7320.
[121] *Ibid.*
[122] *See, e.g.*, SYNG-PQ-20736297 and SYNG-PQ-22035417.
[123] SYNG-PQ-37237312 at 7321.
[124] SYNG-PQ-00068000.
[125] SYNG-PQ-00073357.

Exponent employee, and Syngenta staff, in which Li discusses her efforts to have the paper discourage anyone from thinking paraquat could cause PD.

She writes to Nick Sturgess,[126] telling him to "read the poster carefully," that some results of paraquat/maneb (another pesticide) exposure "are more consistent with PD (or at least that's how they'll be interpreted). So we'll never be able to argue [that paraquat doesn't cause PD] solely on the basis of toxicology alone." She asks Syngenta to provide human exposure data because "general statements will be regarded as hand-waving arguments." In a subsequent email[127] she tells Sturgess that she can't ignore the results of Dino Di Monte's study and therefore can no longer assert that "there is a 1000 fold difference between doses causing neurotoxicity and the chronic RfD [reference dose]" and again asks for Syngenta's help with data so she can make paraquat look less harmful. A few days later she sent another email[128] where she talked about studies linking paraquat exposure to PD and wrote, "it may be possible to weaken its direct association with PD."

The close ties with Exponent continue into 2006. Li is funded to do a study on paraquat by a UK agency, and John Bembridge writes in an email (SYNG-PQ-04110433):

> I would support working with Exponent on this as it helps ensure the science is focussed [sic]. The only area I would think about is how we were acknowledged in any report in case we wanted it to appear as independent work that we could quote in the future or one that we wanted to distance ourselves from.

The strategy continues to be applied by Syngenta through its engagement of an "external epidemiology team" or EET. Through several strategic literature reviews, in which they reviewed and interpreted the studies to date, the members of the EET continually concluded that while some evidence might suggest a causal relationship between paraquat and PD, there was too much uncertainty to determine if it was true, and that more research was needed. Manufacturing uncertainty about scientific evidence is also a tactic that was often used by the tobacco industry and is a specialization of product defense firms. Syngenta convened a meeting with the EET in Boston on March 2, 2009. At the meeting were Jack Mandel of Exponent (although he was identified as being with the University of Toronto then) and four other academics. The report of the meeting (in a memo marked "CONFIDENTIAL AND PRIVILEGED COMMUNICATION") described how the EET would write another review paper to review the scientific literature on PD risk factors *other* than paraquat, with the aim of publishing it within 12 months.[129] This is another tactic used by the tobacco industry—identify everything else that could possibly cause the disease that your product causes, to make your product look safe.

They also discussed a large study being conducted by the U.S. National Cancer Institute, sometimes called the AgHealth Workers Study or the AHS. The plan hatched at that meeting was that if the AHS found no relationship between paraquat and PD, no additional studies would be needed. But if the NCI found a link, Syngenta would have to undertake an actual study (rather than just critique NCI's findings). In other words, the product defense scientists who made up the

[126] SYNG-PQ-00406724.
[127] SYNG-PQ-01739954.
[128] SYNG-PQ-20791944.
[129] SYNG-PQ-04981149.

EET believed that their job was to defend paraquat, not produce impartial, unconflicted science to protect the public health.

That team met again in April 2009[130] in Marlow, UK, along with a group of Syngenta scientists and the "Extended Health Science Team" where it was agreed to move forward with the strategic literature review focusing on other risk factors.

Three months later, Syngenta and Mandel signed a consulting agreement in which Syngenta would pay Mandel $160,000, and he would hire the others as his subcontractors.[131] The review paper was accepted for publication in a supplement of the European Journal of Epidemiology in 2010 and published in 2011.[132] As planned, this paper reviewed many risk factors for PD, mentioning paraquat as only one of many possible exposures associated with PD, with the results from pesticide exposure being less conclusive than some of the other risk factors. In this study, Syngenta's funding was disclosed.

Mandel also produced another literature review for Syngenta criticizing the AHS and two specific studies that suggested a link between paraquat and PD. In this paper, Mandel identified as working for Exponent.[133] This paper included the conflict disclosure:

> This work was funded by an unrestricted grant from Syngenta, Inc. The content of this paper is the sole responsibility of the authors. The authors have previously served as paid consultants to Syngenta, Inc. The content of the paper has been under the full control of the authors for the duration of this effort.

But this review *was* done with Syngenta's input. In February 2011, there is a back-and-forth email exchange in which various Syngenta staff tell Mandel which members of the EET Syngenta would like to see named as co-authors of the paper.[134]

Syngenta's relationship with Exponent continues with a consulting agreement signed in 2012. The agreement includes the clause asserting that "if our mutual efforts hereunder result in scientific publications, the timing, authorship, and content of such publications shall be mutually agreed upon by the parties."[135] This sort of relationship would bar scientists from publishing in any of the leading medical journals; the editors of these journals have asserted that they will not review or publish articles based on studies that are conducted under conditions that allow the sponsor to withhold publication.[136]

Exponent authors then published another strategic literature review, in this case criticizing studies that used geographically modeled environmental exposure estimates—undoubtedly because

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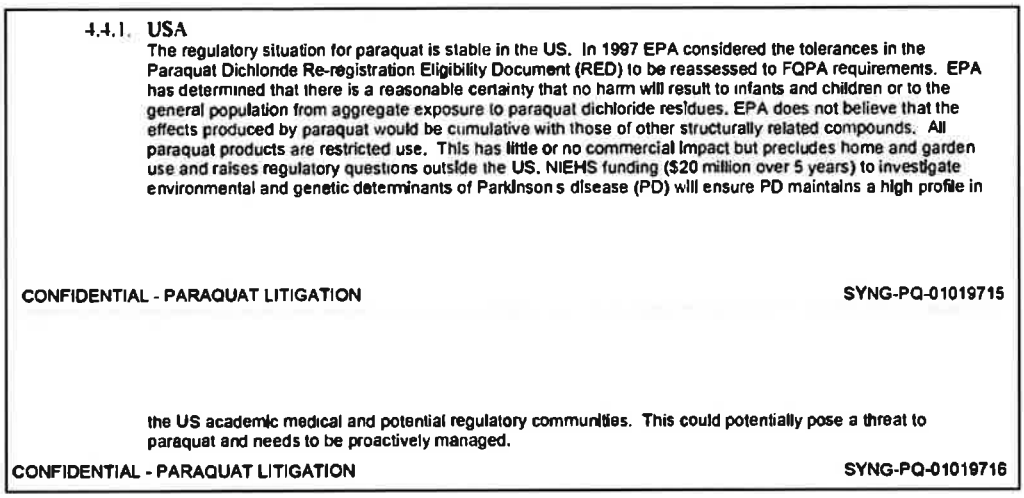
[130] SYNG-PQ-04982646.
[131] SYNG-PQ-01058471.
[132] SYNG-PQ-01189788.
[133] https://www.sciencedirect.com/science/article/abs/pii/S0273230011 001978; SYNG-PQ-00032310.
[134] SYNG-PQ-06900382.
[135] SYNG-PQ-29714824.
[136] http://www.icmje.org/news-and-editorials/update_spon_sep2001.html

several studies using this method had found paraquat exposure to be associated with increased risk of PD.[137]

Notable in the next document is a discussion of funding of independent research by the National Institute of Environmental Health Sciences as something that could "potentially pose a threat to paraquat" and would need to be managed. This suggests the authors recignized that high quality, independent research could easily show that paraquat did indeed increase risk of PD.

SYNG-PQ-01019708



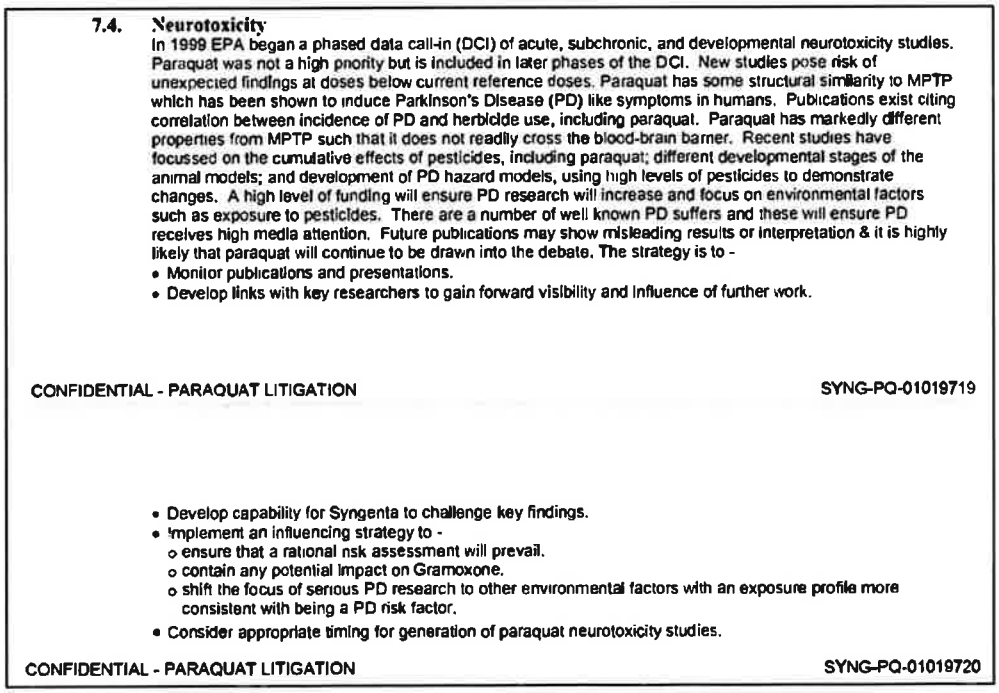
4.4.1. USA

The regulatory situation for paraquat is stable in the US. In 1997 EPA considered the tolerances in the Paraquat Dichlonde Re-registration Eligibility Document (RED) to be reassessed to FQPA requirements. EPA has determined that there is a reasonable certainty that no harm will result to infants and children or to the general population from aggregate exposure to paraquat dichloride resldues. EPA does not believe that the effects produced by paraquat would be cumulative with those of other structurally related compounds. All paraquat products are restricted use. This has little or no commercial impact but precludes home and garden use and raises regulatory questions outside the US. NIEHS funding ($20 million over 5 years) to investigate environmental and genetic determinants of Parkinson s disease (PD) will ensure PD maintains a high profile in

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQ-01019715

the US academic medical and potential regulatory communities. This could potentially pose a threat to paraquat and needs to be proactively managed.

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQ-01019716



7.4. Neurotoxicity

In 1999 EPA began a phased data call-in (DCI) of acute, subchronic, and developmental neurotoxicity studies. Paraquat was not a high priority but is included in later phases of the DCI. New studies pose risk of unexpected findings at doses below current reference doses. Paraquat has some structural similarity to MPTP which has been shown to induce Parkinson's Disease (PD) like symptoms in humans. Publications exist citing correlation between incidence of PD and herbicide use, including paraquat. Paraquat has markedly different properties from MPTP such that it does not readily cross the blood-brain barrier. Recent studies have focussed on the cumulative effects of pesticides, including paraquat; different developmental stages of the animal models; and development of PD hazard models, using high levels of pesticides to demonstrate changes. A high level of funding will ensure PD research will increase and focus on environmental factors such as exposure to pesticides. There are a number of well known PD suffers and these will ensure PD receives high media attention. Future publications may show misleading results or interpretation & it is highly likely that paraquat will continue to be drawn into the debate. The strategy is to -

- Monitor publications and presentations.
- Develop links with key researchers to gain forward visibility and influence of further work.

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQ-01019719

- Develop capability for Syngenta to challenge key findings.
- Implement an influencing strategy to -
  - ensure that a rational risk assessment will prevail.
  - contain any potential impact on Gramoxone.
  - shift the focus of serious PD research to other environmental factors with an exposure profile more consistent with being a PD risk factor.
- Consider appropriate timing for generation of paraquat neurotoxicity studies.

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQ-01019720

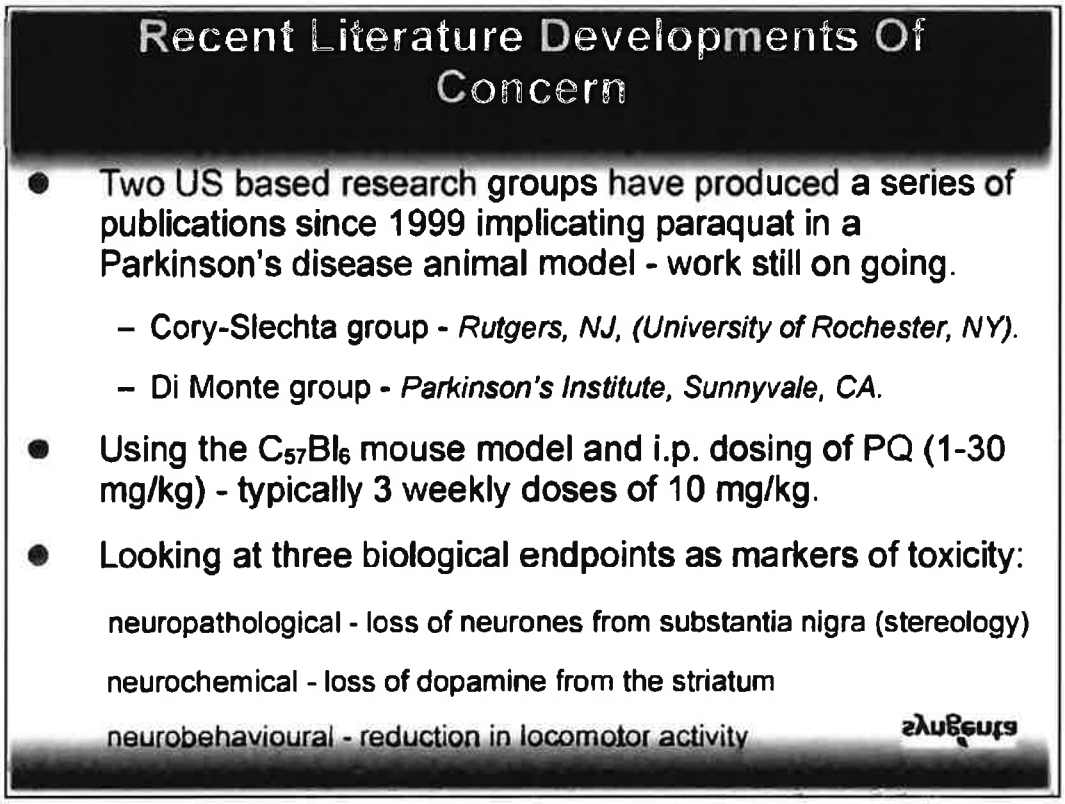
[137] https://www.tandfonline.com/doi/full/10.3109/10408444.2014.902029

2. Techno-Regulatory meeting November 2004

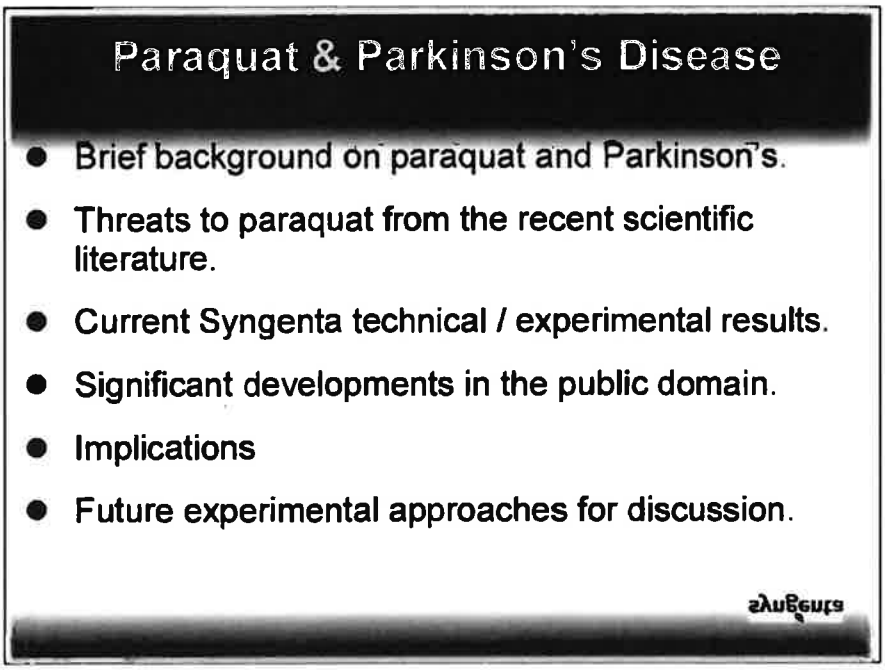
As discussed earlier, in the late 1990s and early 2000s, published research began linking paraquat and Parkinson's disease. This research used newer technology (stereology) to count neurons. Internal studies in 2003 (discussed later) appear to have been the start of Syngenta's internal scientific review of that literature. By at least by November 2004, Syngenta began laying out a corporate strategy for responding to that emerging threat at a "Techno-Regulatory" Meeting.

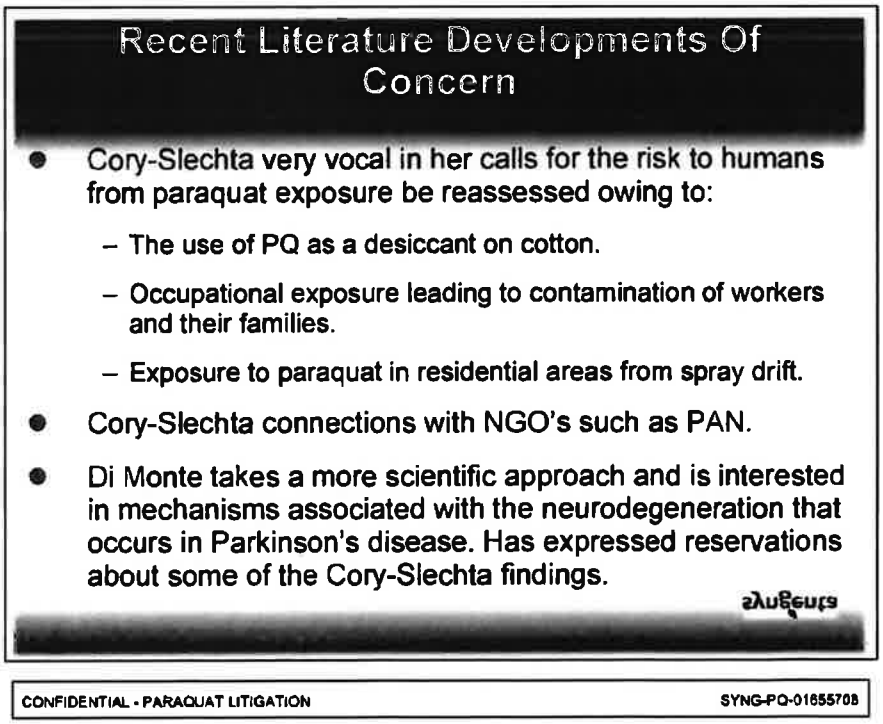
There were two separate research groups of concern: the Cory-Slechta group at the University of Rochester in New York and the Di Monte group at Parkinson's Institute in California. Both groups had found Parkinson's-like symptoms in the Charles River black mouse after injecting the mice with paraquat.

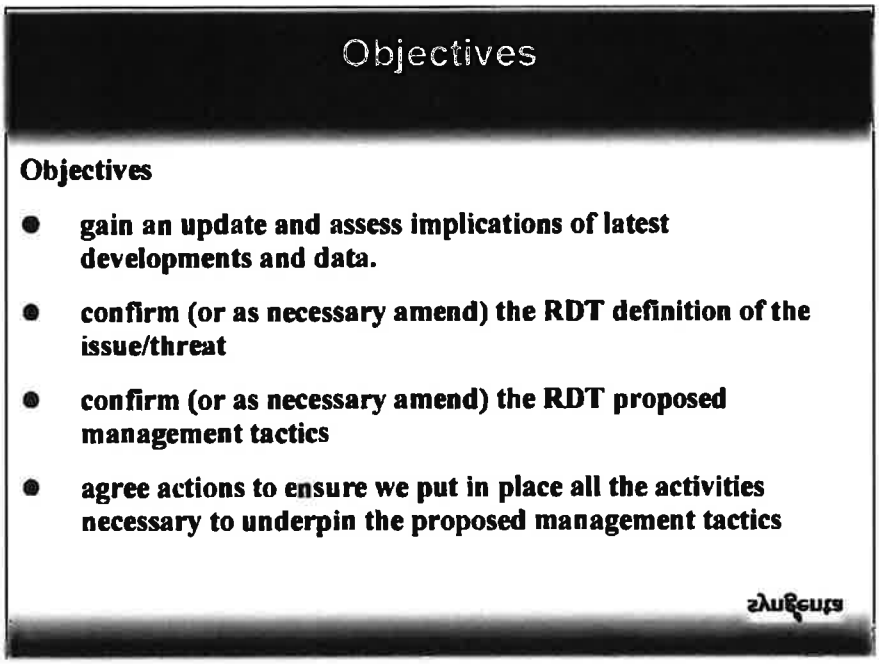
SYNG-PQ-01655689



Syngenta considered the work of the Cory-Slechta and Di Monte groups to be "threats." So, the purpose of the Techno-Regulatory meeting in November 2004 was to lay out Syngenta's strategy for responding to the emerging "threat" (as defined by the Regulatory Development Team (RDT)) posed by the paraquat/Parkinson's research of the Cory-Slechta and Di Monte groups.

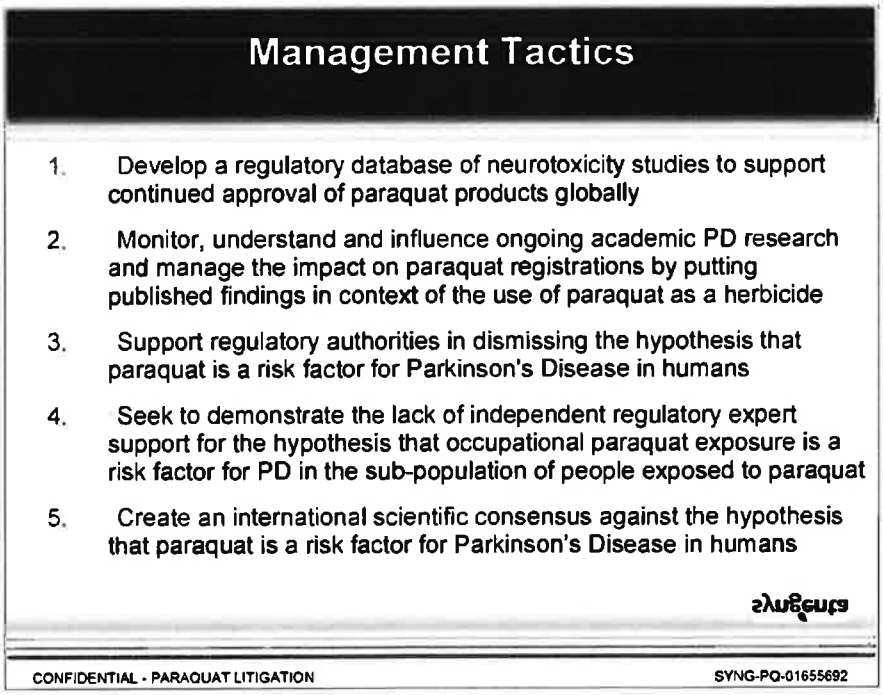






3. Tactics for responding to the "threat"

Syngenta's tactics for responding to the "threat" posed by Cory-Slechta's and Di Monte's research included:



Much of the subsequent work published in the scientific literature by product defense consultants hired by Syngenta follows the objectives and strategy laid out in this document. It is also clear from this and other documents that the purpose of the Techno-Regulatory Team's job was to defend paraquat and convince regulators and scientists that paraquat exposure was not a risk factor for Parkinson's disease, rather than try to ascertain the truth about that relationship. At a June 2003 meeting, the Regulatory Development Team concocted a scheme to have Di Monte "publicly comment on the excessive claims of the Cory-Slechta papers" so that Syngenta could have a "referee" intervene to "resolve" the dispute. SYNG-PQ-01662351-56.

The comments were made that it is in Syngenta's interest

- if Di Monte would publicly comment on the excessive claims of the Cory-Slechta papers
- if Beaman remains active, promotes and gains support for his soil bacteria causative model and publicly challenges the PQ causative model
- if a third party emerged to figuratively act as a referee between the Di Monte and Cory-Slechta groups different perspective of PQ (academic model v potentially causative contributory agent)
- if greater attention was given to the uncertainties in the epidemiology linking PD to pesticide use

Action	Tim Pastoor	To work with Nick Sturgess and Mike Clapp to work up a project plan and resource needs to develop and implement a PD influencing strategy in the USA. To include definition of the targets of the influencing programme.	Draft by end Aug 2003 for inclusion is 2004 development resource plan

SYNG-PQ-01662356

Syngenta's response to independent scientific literature became more sophisticated over time. For example, it formed a "PQ SWAT" Team for responding quickly to any publication that linked paraquat to Parkinson's disease or raised other issues of concern.

502(d)-001590.0001

PILT PQ Communications Management Presentation 3/8/11

PQ COMMUNICATIONS MANAGEMENT

1. Proactive strategic communications: the release of new data or studies that Syngenta controls
   - Situation allows lead time to plan communications strategy and messages adequately
2. Issues management: new studies and publication alleging PQ/PD link that Syngenta has not participated, or news articles or monitoring analysis that cause concern – PQ SWAT Team
   - No advance warning or planning

Additional SWAT documents appear in Appendix A.

D. Syngenta suppresses research

1. Syngenta's failure to report the Marks studies

In 2003, Syngenta decided to conduct research internally to see if the results of the Cory-Schlecta and Di Monte groups could be "replicated." Dr. Louise Marks was assigned the task, and in her first study, she found no statistically significant loss of dopaminergic neurons. Dr. Marks had reservations about this result, concerned that it might have been due to outdated neuron-counting technology. Dr. Marks conducted two more studies and also paid a visit to Dr. Di Monte's lab where she learned about the state-of-the-art neuron-counting technology that she then applied in her second and third studies.

The purpose of the second study[138] was to determine whether the results of her first study could be reproduced. [139] The difference between the two studies were the methodologies and technology Dr. Marks used. In her second study she "used one of the most widely used and accurate stereology systems currently available and the methodology was refined to further improve the accuracy of the cell count data," not the non-automated older stereology software used in the first study. In this second study, Dr. Marks reported a statistically significant reduction in dopaminergic neurons.

Dr. Marks attributed the difference in findings to the different methodologies and technologies used in the two studies. Her second study replicated results of independent researchers in the published literature. Dr. Marks' finding of a statistically significant reduction in dopaminergic neurons in the subtantia nigra of the Charles River black mouse was a finding the EPA "might regard as raising concerns" about the continued registration of paraquat or about the appropriate terms and conditions of continued registration of paraquat. Her finding is "information regarding unreasonable adverse effects on the environment of the pesticide" because it is information about an "unreasonable risk to man or the environment" posed by paraquat. Nevertheless, Syngenta failed to report Dr. Marks's study for fifteen years.

> With respect to the apparent cell loss observed in the SNpc. the results from this present study differ from the findings of a previous CTL study (CTL/XM7229/RES/REPT), where 10 mg/kg PQ dichloride, dosed once weekly for three weeks. failed to produce any significant signs of nigrostriatal toxicity, with only a small (4%) but statistically non-significant reduction in TH cells in the SNpc. The failure to detect a significant degree of cell loss in the first study is likely to be attributable to the differences in the stereology methodology. software and hardware used in the two separate studies. The present study used one of the most widely used and accurate stereology systems currently available and the methodology was refined to further improve the accuracy of the cell count data. These changes to the stereology hardware and software were implemented following a visit to the Parkinson's Institute in California and discussions with the DiMonte group. This is in contrast with the original set up used in the study XM7229 which relied on counts being carried out using a non automated stage and used much older stereology software. Subsequent retrospective re-analysis of the neuronal cell count assessment was not possible owing to the deterioration of the XM7229 study slides over the intervening period.
>
> SYNG-PQ-00116808

[138] SYNG-PQ-00116782 – Paraquat Dichloride Hydrate – Investigating Reported Paraquat Neurotoxicity in the Charles River C57 Black Mouse – XM7258/Research/Report (L. Marks 6.21.2007).
[139] *Ibid.* at 6791

The purpose of Dr. Marks' third study[140] was to investigate whether the loss of dopaminergic neurons in the substantia nigra observed in her second study could be further enhanced by increasing the frequency of dosing. Dr. Marks again found a statistically significant loss of dopaminergic neurons, but concluded that the increased dosing frequency did not result in greater magnitude of cell loss. In other words, Marks confirmed the findings of her second study. .[141]

Internally, Lewis Smith (one of Dr. Marks's superiors) desired to aggressively challenge Dr. Marks' findings. Dr. Mark and Dr. Sturgess (Dr. Marks's direct supervisor) discussed ways of challenging the findings, one of which was to repeat the study in different strains of mice less sensitive to paraquat, presumably in hopes of generating a negative result. But Smith, Sturgess and Marks decided not to do that because "this would generate a PRF [potentially referable finding] since no one else has dosed [paraquat] to these strains."

SYNG-PQ-01981435 – Thoughts on Challenging the PQ & C57Bl6 Mouse Model (12.6.2004)

> - If we were concerned that the pigmented mouse was more sensitive to PQ than other strains, one option would be to dose 10 mg/kg PQ to variety of different mouse strains including BALB/c, Swiss Webster and CF1, and observe the extent of the neuronal cell loss. However, this would generate a PRF since no one else has dosed PQ to these strains.
>
> SYNG-PQ-01981435

Instead of reporting Marks's findings to the EPA, they came up with a supplemental research program to cast doubt on Marks's earlier finding that paraquat was neurotoxic. Marks undertook yet another study[142] to test whether the results were durable over time. This study, too, was consistent with Marks's previous findings.

> **2.1 Purpose**
>
> The aim of this study was to investigate the time course and potential reversibility of nigrostriatal effects following 3 weekly injections of 10 mg/kg paraquat dichloride by assessing dopaminergic cell loss in the SNpc and concentrations of striatal dopamine and its metabolites at 7, 28 and 90 days after the final dose of paraquat.
>
> SYNG-PQ-00492793

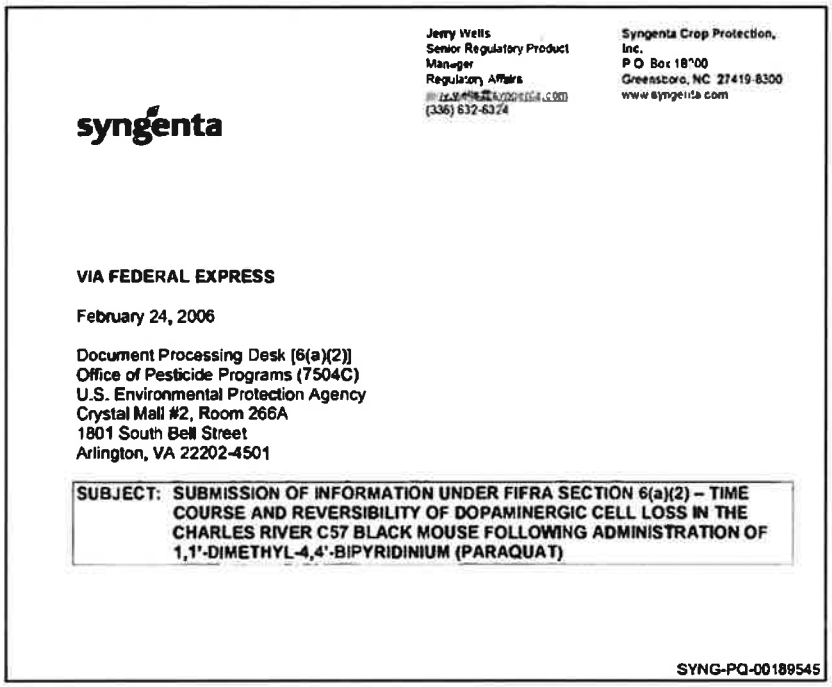
The degree of dopaminergic neuron loss at 28 and 90 days was similar to the loss at 7 days in Dr. Marks' earlier studies. [143] The loss at those intervals was also consistent with reports in the literature. Syngenta did report one of the findings of this study to the EPA. The result at 90 days had not already been reported in the scientific literature, so Syngenta had no choice but to report that finding to the EPA. In fact, all of the findings of this fourth study – just like the second and third

---

[140] SYNG-PQ-00490903 – Paraquat Dichloride Hydrate – Investigating Reported Paraquat-Induced Dopaminergic Neurotoxicity in the Charles River C57 Black Mouse: The Neurochemical, Neuropathological and Neurobehavioral Effects of Increasing the Dosing Frequency of Paraquat – XM7371 (Marks' third study).
[141] *Ibid.* at 0911-12.
[142] SYNG-PQ-00492785 – Paraquat Dichloride Hydrate – Investigating the Time Course and Reversibility of Dopaminergic Cell Loss in the Charles River C57 Mouse Following Administration of Paraquat – XM7480/Research/Report (Marks' fourth study).
[143] *Ibid.* at 2792.

studies – were reportable under 40 CFR § 159.158, because 1) Dr. Marks was a qualified expert; or 2) she was a Syngenta employee. Moreover, Syngenta downplayed the significance of even the one finding it did report. It told the EPA the ***dose*** of paraquat used in the experiment was "an extremely high systemic does that is unlikely, if not impossible, to achieve in humans under an acceptable use scenario." Here, we see in action Syngenta making the dose argument when causation was not only undeniable, Syngenta was itself reporting that causation to the EPA.

SYNG-PQ-00189545 – Submission of Information Under FIFRA Section 6(a)(2)



Jerry Wells
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Regulatory Affairs
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syngenta

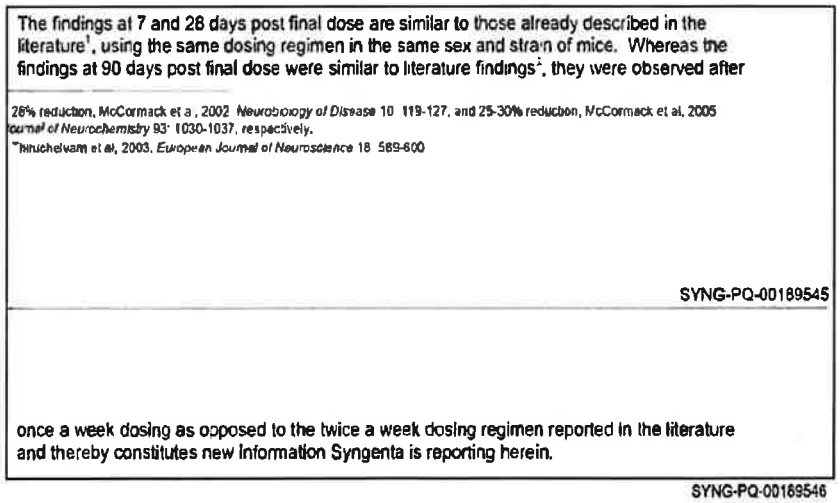
VIA FEDERAL EXPRESS

February 24, 2006

Document Processing Desk (6(a)(2))
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Crystal Mall #2, Room 266A
1801 South Bell Street
Arlington, VA 22202-4501

SUBJECT: SUBMISSION OF INFORMATION UNDER FIFRA SECTION 6(a)(2) – TIME COURSE AND REVERSIBILITY OF DOPAMINERGIC CELL LOSS IN THE CHARLES RIVER C57 BLACK MOUSE FOLLOWING ADMINISTRATION OF 1,1'-DIMETHYL-4,4'-BIPYRIDINIUM (PARAQUAT)

SYNG-PQ-00189545



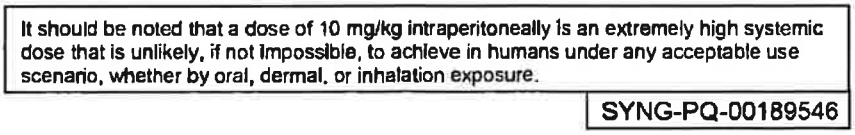
The findings at 7 and 28 days post final dose are similar to those already described in the literature[1], using the same dosing regimen in the same sex and strain of mice. Whereas the findings at 90 days post final dose were similar to literature findings[2], they were observed after

28% reduction, McCormack et a , 2002 *Neurobiology of Disease* 10 119-127, and 25-30% reduction, McCormack et al, 2005 *Journal of Neurochemistry* 93: 1030-1037, respectively.
[2]Thiruchelvam et al, 2003. *European Journal of Neuroscience* 18 589-600

SYNG-PQ-00189545

once a week dosing as opposed to the twice a week dosing regimen reported in the literature and thereby constitutes new information Syngenta is reporting herein.

SYNG-PQ-00189546

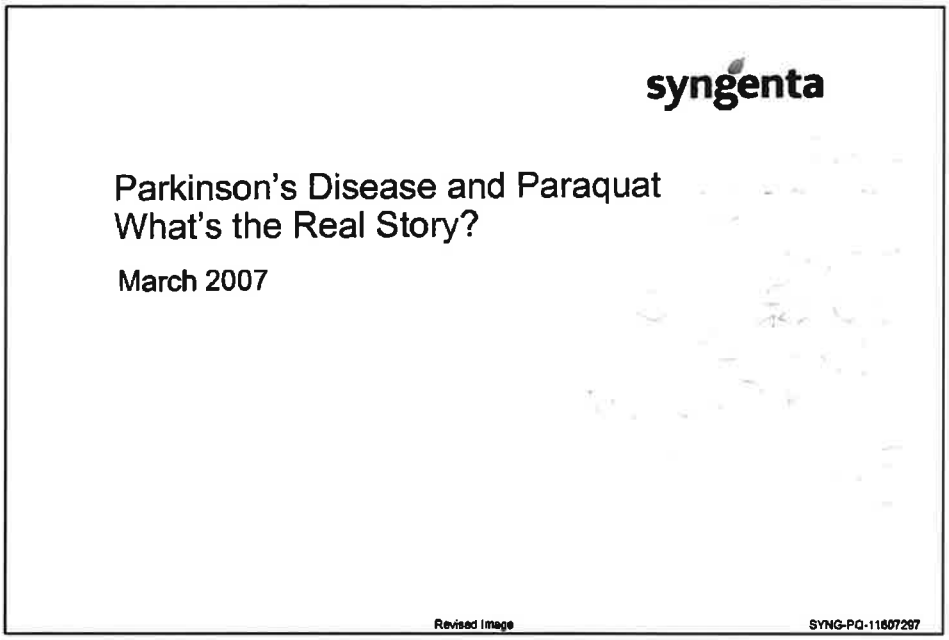


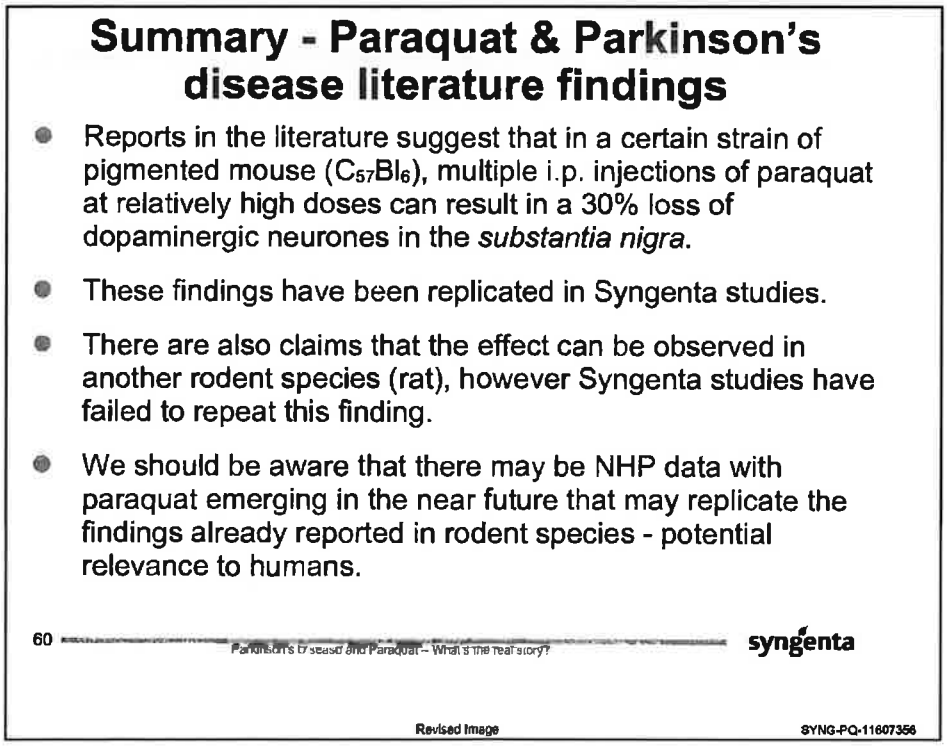
It should be noted that a dose of 10 mg/kg intraperitoneally is an extremely high systemic dose that is unlikely, if not impossible, to achieve in humans under any acceptable use scenario, whether by oral, dermal, or inhalation exposure.

SYNG-PQ-00189546

Even before Dr. Marks finalized her written reports in June 2007, Syngenta recognized internally that the literature reporting loss of dopaminergic neurons in the substantia nigra of the Charles River black mouse after administering paraquat were "findings [that] have been replicated in Syngenta studies."

SYNG-PQ-11607297





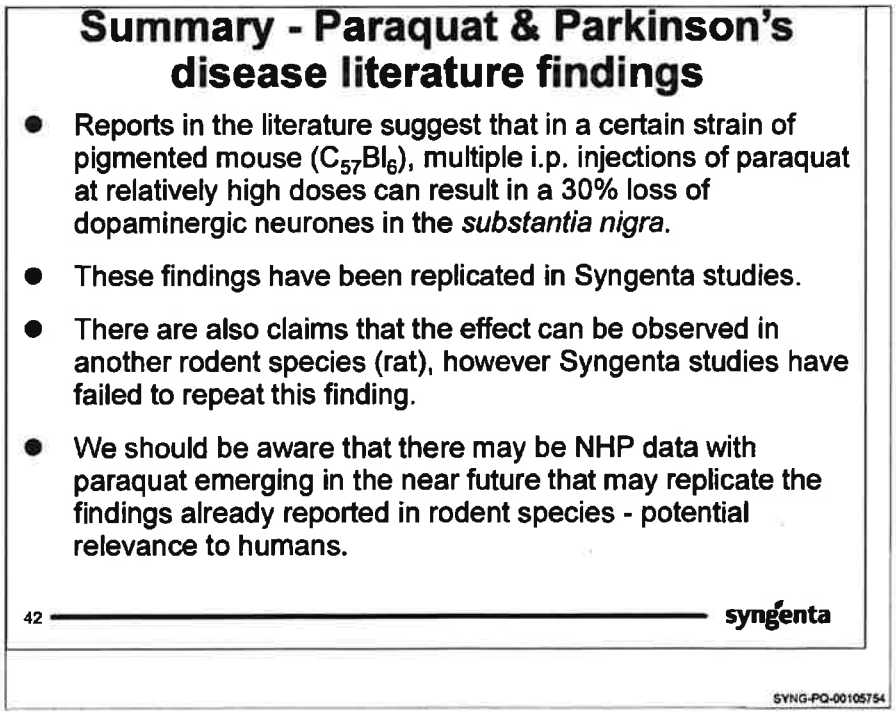
2. Syngenta's failure to report the Di Monte studies

In April 2009 at a Syngenta meeting in Marlow, England, Dr. Di Monte gave a presentation of preliminary results from his studies with paraquat in squirrel monkeys. At that meeting, Dr. Di Monte reported the following observations from his "preliminary results":

- loss of striatal dopamine (which is associated with Parkinson's disease)
- up-regulation of alpha synuclein (the major constituent of Lewy bodies and a pathogenic hallmark of Parkinson's disease)
- a change in neuromelanin (and an accumulation of neuromelanin in dopaminergic neurons is suspected to play a role in the development of Parkinson's disease)
- a loss of dopamine-producing function

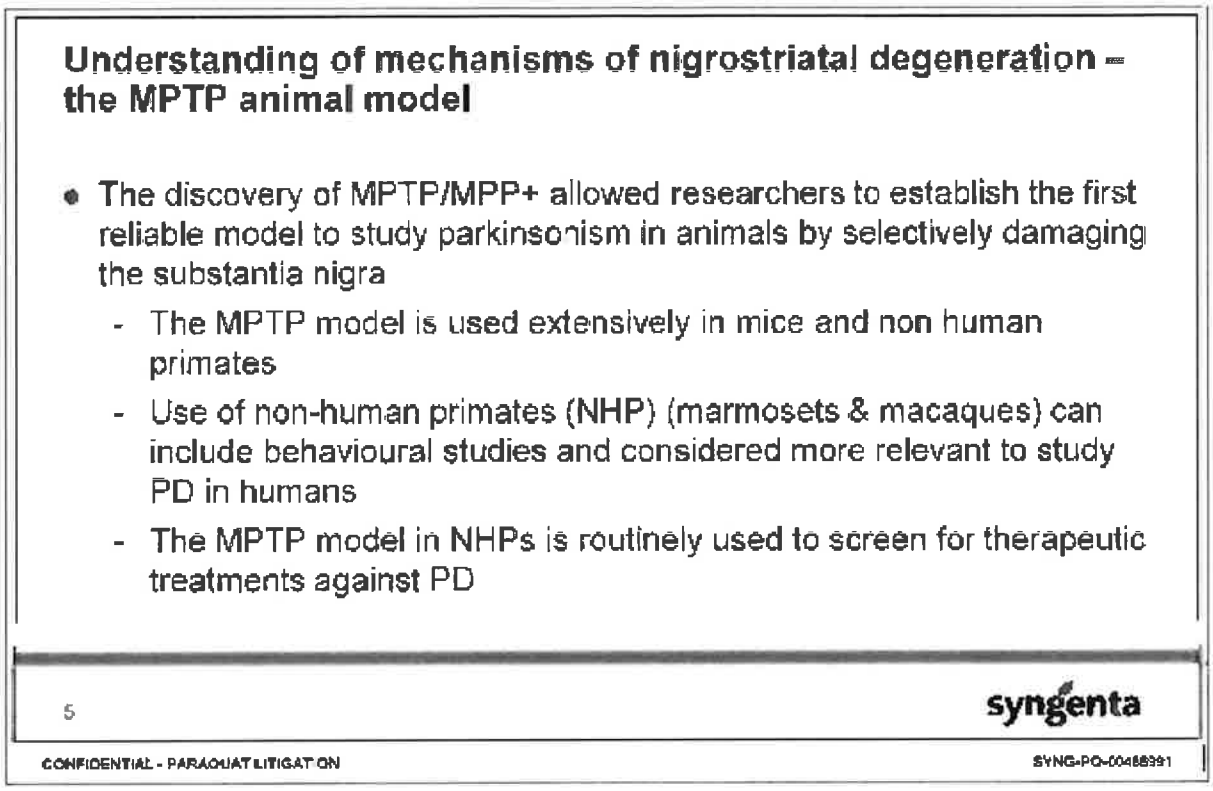
SYNG-PQ-01305484; *see* SYNG-PQ-01117480 (Paraquat Health Science Team Action Minutes from Marlow Meeting, 20 & 21 April 2009). In fact, Syngenta had learned of Dr. Di Monte's non-human primate findings two years earlier. (*See* SYNG-PQ-01739155 (5/11/2007 email from N. Sturgess to B. Elliott)). Reference was also made to Di Monte's primate research at an April 2008 Syngenta meeting in Atlanta. Despite its knowledge of the Di Monte primate studies, Syngenta never reported them to the EPA.

SYNG-PQ-00105713 (presentation slide from Atlanta Meeting February 2008)



And, as the document below confirms, Syngenta knew that non-human primate studies were considered more relevant to humans than mice.

SYNG-PQ-00486987 (Update on Syngenta's Research Program)



Understanding of mechanisms of nigrostriatal degeneration – the MPTP animal model

- The discovery of MPTP/MPP+ allowed researchers to establish the first reliable model to study parkinsonism in animals by selectively damaging the substantia nigra
  - The MPTP model is used extensively in mice and non human primates
  - Use of non-human primates (NHP) (marmosets & macaques) can include behavioural studies and considered more relevant to study PD in humans
  - The MPTP model in NHPs is routinely used to screen for therapeutic treatments against PD

5

syngenta

CONFIDENTIAL - PARAQUAT LITIGATION

SYNG-PQ-00486991

3. Syngenta's failure to report its own primate brain residue study

Syngenta conducted paraquat residue studies on the brain tissue of the squirrel monkeys used in Dr. Di Monte's studies. Syngenta confirmed that paraquat was present in the brain tissue. SYNG-PQ-00044965 (Analysis of Brain Samples from Paraquat-Exposed Monkeys). Dr. Travis referred the finding of this study to the Syngenta Potentially Referable Findings Approach Committee.

SYNG-PQ-01547528 – Syngenta Crop Protection Potentially Referable Findings (PRF)

The monkey brain tissue samples exhibited paraquat residues which ranged from 0.007 µg/g to 0.256 µg/g, except samples 664, 666 and 732 which were < LOQ.

SYNG-PQ-00044971

PRF No. | THS1120

Page 1 of 3

SYNGENTA CROP PROTECTION

POTENTIALLY REFERABLE FINDINGS (PRF) FORM FOR PRODUCT SAFETY

Part 1 – Typically to be completed by Study Manager/Project Leader

CHEMICAL/PRODUCT NAME: Paraquat dichloride

STUDY TITLE: More than one – see below

LABORATORY: More than one - see below STUDY NO:

REPORT: DRAFT: [ ] FINAL: [ ] IF FINAL, DATE ISSUED.

OTHER SOURCE:

1a. STUDY MANAGER TO GIVE A BRIEF DESCRIPTION OF THE FINDINGS (INCLUDING THE REASON FOR A POSSIBLE REFERRAL):

SYNG-PQ-01547528

Name of Study Manager/Originator: Kim Travis Date: 28 June 2011

SYNG-PQ-01547528

The proportion of a dose of paraquat that reaches the brain is very small. This document concerns the emerging data on the kinetics of this small amount of paraquat in the brain. The body of data on this subject, though initially indirect and incomplete, has now been examined in more detail and expanded across species in more recent studies and should now be considered in the PRF process

SYNG-PQ-01547528

Data has existed for some years that although the paraquat concentration in the brain of the rat declines over the first 24 hours after dosing (Dey et al, 1990 Naylor et al, 1995), the amount remaining in the brain at 24 hours after dosing declines more slowly (Dey et al, 1990 Widdowson et al, 1996). More recently, Syngenta conducted a radiolabelled kinetic study in the C57Bl6/J mouse, which showed that paraquat is only slowly eliminated from the brain of this animal (Gledhill, 2008). Shortly afterwards this was independently confirmed in the literature (Prasad et al 2007). These studies and later work have indicated that the half-life of paraquat in the brain of the C57Bl6/J mouse is about 21 days. More recently still, we have conducted a radiolabelled study in the rat which demonstrates a terminal half-life in brain of about 28 days (McBride et al, 2011) We have also analysed samples of squirrel monkey frontal cortex from a study conducted independently by Prof di Monte, which shows that the paraquat concentration in the brain samples did not measurably decline between samples reported to have been taken 2 and 8 weeks after a fixed program of paraquat dosing (Ray, 2011 and di Monte 2011 pers. comm.).

SYNG-PQ-01547528

Part 2 – To be completed by PRF Approach Committee

2a. PRF APPROACH COMMITTEE COMMENTS:

Studies of the kinetics of paraquat in the brain across a range of species were considered. The committee considered that the findings do not represent an adverse effect or a pre-cursor to an adverse event. Therefore the findings do not meet the technical criteria for referral as described in the Product Safety PRF Criteria for Referral Guidance Document (version 4 dated 16th Feb 2009).

SYNG-PQ-01547529

The committee concluded without explanation that the finding of paraquat in Dr. Di Monte's monkey brains did "not represent an adverse effect or a pre-cursor to an adverse event." It did so despite the Committee's acknowledgment to Brazilian regulators in 2012 that "use of non-human primates (NHP) (marmosets and macaques)" are "considered more relevant to study PD in humans." *See* SYNG-PQ-00486987 Update on Syngenta's Research Program (previously cited). The committee's 2011 unexplained conclusion also conflicted with its own unanimous determination in May 2009 that Dr. Di Monte's "brain findings in the non-human primate were unanimously agreed as constituting new data."

SYNG-PQ-02601795

The brain findings in the non-human primate were unanimously agreed as constituting new data. The participants noted that the study had not yet been completed, peer reviewed or published and that the data, by Dr Di Monte's own admission, required further verification. The participants also noted that the toxicological significance of the apparent phenotypic changes is unclear. On the basis of the preliminary nature of the findings and the lack of obvious adverse consequence of the findings in the brain the data do not meet the necessary technical criteria for referral.

SYNG-PQ-02601796

The reason the committee gave for not reporting Dr. Di Monte's monkey brain findings to the EPA in 2009 was "that the study had not yet been completed, peer reviewed or published and that the data, by Dr. Di Monte's own admission, required further verification." Two years later, in 2011 after Syngenta scientists completed their study of those same monkey brains and found paraquat in that brain tissue, the committee could no longer justify withholding that adverse information due to

the incompleteness of the study. Instead, the committee claimed that Syngenta's own findings of paraquat in the monkey brains was not reportable because "the findings do not represent an adverse effect or a pre-cursor to an adverse event." Syngenta here conveniently leaves out Di Monte's other key findings they should have reported. In 2011, the Syngenta Executive Committee rejected a proposal to study alpha-synuclein, over the objections of Charles Breckenridge. In an email relaying this to Breckenridge, Phil Botham admits that "most people would say that increased synuclein expression is associated with an adverse effect," (SYNG-PQ-01640738), and in fact, Di Monte presented to Syngenta that PQ caused an upregulation of alpha-synuclein in monkey brains (cited earlier at SYNG-PQ-01117480). So at the very same time Syngenta is again declining to report Di Monte's findings to the EPA because they "do not represent an adverse effect or a pre-cursor to an adverse effect," Syngenta's own scientists know this not to be true.

E. Syngenta seeks to shift blame to plaintiffs for failing to take safety precautions

Although Syngenta has known for years from its own studies that paraquat users from all over the world routinely used the chemical without using all—and often not any—label-prescribed personal protection equipment,[144] it was quick to assign blame to Plaintiff Ronald Niebruegge during his deposition. Despite this explicit knowledge of how paraquat was being handled and applied throughout the world, Syngenta's counsel conducted the following examination of Plaintiff Ronald Niebruegge during his discovery deposition in this case:

> [Page 122]
>
> Q. You were also aware throughout the time that you used or applied paraquat, across your whole career, that you should not inhale the paraquat spray mist, right?
>
> * * *
>
> A. What was—as a matter of practicality, can you explain to me how you can spray it in the field and not inhale it?
>
> Q. You can wear a respirator, right, sir?
>
> A. Not when we were actually spraying it, no.
>
> Q. You could have worn a respirator if you'd wanted to, right?
>
> A. I guess we could have worn a respirator, but I don't—I don't really recall on the early labels if it said we had to wear a respirator.
>
> [Page 126]
>
> Q. ... And so you were aware, at least from the mid '80s onward, that if you thought there was a danger that you might be exposed through inhalation, that you should wear a face mask capable of filtering spray droplets, right?
>
> A. My understanding of what it is saying there is I needed to wear that equipment when I was loading and mixing it. And when I'm actually out in the field spraying it, I don't think it is required.

[144] *See* Appendix B.

Q. You testified a moment ago, something to the effect that if you are out in the field, you didn't know how one could avoid inhaling spray droplets. Something to that effect. Do you remember that?

A. Yes.

Q. Was that your perception or your understanding throughout your career about whether you were or weren't being exposed to inhalation to spray droplets?

[Page 127]

A. I don't know how you could – you couldn't operate a sprayer with all this stuff on it all day long. Everybody that used this product was out there spraying it without having a space suit on the whole time they were using it.

Q. So it was your understanding, throughout the time, from the late '60s onward, in your farming career, that if you were applying paraquat in the fields, you were likely inhaling it? Is that fair?

A. I didn't think I was inhaling it all the time, no.

Q. Sometimes?

A. When I was just sitting up on the tractor with the sprayer running behind me, I didn't think I was inhaling it, when it was 20 feet away from me, wherever it was being sprayed, unless you turned around in the wind.

Q. So it was your understanding from the late '60s onward in your farming career that you were at risk, at least, of inhaling paraquat droplets while you were applying the product in the field? Is that fair?

A. You are at risk of inhaling whatever [Page 128] you are applying in the field when you are spraying.

Q. Including paraquat, right?

A. Yes.

Q. Now, you understood, also, throughout your farming career, that one thing you could have done to avoid any risk of inhaling paraquat or other chemicals is to wear a respirator that would filter out those particles, right?

A. Well, I guess we could have, but we didn't feel it was necessary.

Q. My question right now is not whether you felt it was necessary. But you were aware, at least conceptually, from the 1960s onward, that if you wanted to eliminate the risk of inhaling paraquat particles, you could have worn a respirator, right?

A. I'm not sure we could have found a respirator that was going to protect us out in the [Page 129] field anyway, when you are sweating so bad.

Q. Did you ever try?

A. No. I never tried to wear a respirator. Like I said, when we first started using the product, I don't remember that the label even stated that you were supposed to wear one.

> Q. Leaving aside whatever the label said. But you—you just understood that there were respirators out in the world that could filter out chemicals and—prevent you from breathing them in, right? From the '60s onward, you were aware that that equipment existed in the world, right?
>
> A. We were not aware of what kind of respirators were out there. Only thing we knew about were those dust masks we used around the farm.

True to form, this line of questioning exemplifies the corporate blaming strategy. With knowledge gained over several decades that applicators typically do not wear respirators when applying paraquat and after expressing publicly for many years that respirators are not necessary during application, their counsel repeatedly tries to "blame" Mr. Niebruegge for his own illness.

F. Syngenta has focused on dose, exposure levels and exposure routes because causation is no longer plausibly deniable.

As discussed earlier in the report, once the industry is no longer able to plausibly deny causation, they turn their uncertainty campaign to the question of dose. Syngenta has in recent years resorted to the same tactic to defend paraquat. Dr. Marks confirmed internally what the independent literature had already found—that paraquat is neurotoxic in the mouse.[145] But even before her studies had begun, Syngenta planned to argue the doses used were high and not relevant to humans, in the event she found neurotoxicity.[146] After Dr. Marks confirmed her results with two additional toxicity studies and one methodology study,[147] Syngenta was forced to confront the reality of paraquat's neurotoxicity.[148] Key company scientists were charged with conducting an internal preliminary risk assessment to evaluate whether the then-current reference dose and Acceptable Operator Exposure Level (AOEL) should be revised. Syngenta's answer was no.[149]. Dr. Marks' results were not provided to the EPA to allow them to evaluate user risk.

Syngenta did predict how the EPA would respond to the Marks findings, noting it was "prudent to assume that the effects on substantia nigra will be interpreted by some regulatory authorities as indicative of neurotoxicity." In the absence of robust toxicology data, Syngenta predicted the regulators would set the AOEL approximately at one third the current level to ensure operator safety. But because Syngenta did not share the Marks findings with the EPA, the agency was unaware the AOEL needed to be revised. Syngenta rationalized keeping the EPA in the dark "given the uncertainty of the calculation Product Safety considered the difference not to be significant."[150]

Fearing the EPA might revise the AOEL based on other published studies, Syngenta decided to develop a physiologically-based pharmacokinetic (PBPK) model of human exposure. Syngenta

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[145] SYNG-PQ-00116782 (discussed later in the text).
[146] SYNG-PQ-00493318 at 18 (SYNG-PQ-00493335).
[147] SYNG-PQ-00490903; SYNG-PQ-00492785; SYNG-PQ-00084920.
[148] SYNG-PQ-29640381 at 1 ("this finding is judged to be real and to be related to paraquat treatment").
[149] *Ibid.* ("although the estimated reference dose is approximately 2-fold lower than the current Syngenta reference dose position, given the uncertainty of the calculation Product Safety considers the difference not to be significant").
[150] *Ibid.* at 1-2, 6 (AOEL revised from 0.0005 mg/kg/d to 0.00033 mg/kg/d).

intended to use the model to persuade regulators not to cut the current AOEL, but instead, replace it with a level the company would propose.[151]

> • Conventional risk assessments for the use of PQ, i.e. risk assessments supporting regulatory approvals, will be improved by the new study. Specifically, regulatory PQ operator risk assessments in most countries are based on PQ operator exposure studies, and the results from these are corrected using an assumption that 59% of absorbed PQ is excreted in urine. The new study will supersede this figure, replacing it with a figure much closer to 100%. This will result in greater safety margins being estimated, so supporting the regulatory position of PQ. SYNG-PQ-01208794

Syngenta intended to extrapolate from pharmacokinetic data from rodents and dogs to humans.[152] Its studies found rats and dogs excrete approximately 99% and 95% of low doses of paraquat within the first few days after dosing, meaning only 1% and 5% would remain to harm the animal.[153] Based on this data, Syngenta wanted its human exposure model to predict that humans would excrete 100% of paraquat. But there was a problem: a published study in monkeys had found primates excrete about 59% of paraquat.[154]

> • By obtaining 80% recovery in this type of study scientific community would consider this to be complete meaning no corrections necessary to account for unrecovered dose in 'human urine'
> - *i.e.* 80 % can be assumed to be 100%
> - PBPK model simulations capture the NHP plasma data with 100% urinary excretion
>
> SYNG-PQ-01116651

So Syngenta then conducted a macaque study to prove that primates, like rats and dogs, excrete almost all of the paraquat dose. In the first phases of their study, Syngenta could only recover 80% of the paraquat dose. Kim Travis, the principal investigator, was unperturbed, saying "80% can be assumed to be 100%."[155]

If challenged that the unrecovered paraquat remained in the monkey, he planned to answer there was "no convincing evidence of species differences in excretion." Apparently, Travis discounted the evidence his own study had produced.[156] In the fourth phase of the study, Syngenta found that the monkeys retained 10% of the paraquat.[157] Syngenta considered this evidence that primates were similar to rodents and dogs, even though the rodents and dogs retained only 1% and 5%. This was how Syngenta's model predicted users would absorb only a fraction of a dermal

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[151] SYNG-PQ-01208793 at 2 (SYNG-PQ-01208794).
[152] SYNG-PQ-01117429 at 2 (SYNG-PQ-01117430) (PBPK modelling strategy outlining use of rodent models scaled to man); at 4 (SYNG-PQ-01117432) (conducted an NHP study to demonstrate lack of a fundamental non-primate vs primate difference in the handling of PQ).
[153] *Ibid.* at 12 (SYNG-PQ-01117440).
[154] SYNG-PQ-01208793 at 2 (SYNG-PQ-01208794). ("the new study will supersede this figure [59%], replacing it with a figure much closer to 100% … it is important that the new study is able to supersede the 59% urinary excretion figure … published by third parties many years ago.")
[155] SYNG-PQ-01116637 at 15 (SYNG-PQ-01116651).
[156] *Ibid.* at 15 (SYNG-PQ-01116651). Travis's and his colleagues also dismissed the findings of their own monkey brain residue study (discussed earlier), which demonstrated species difference between primates and rodents in the distribution of paraquat. The half-life of paraquat in the brains of monkeys was greater than six weeks—much longer than that of mice (21 days) and rats (28 days). *See* SYNG-PQ-01116541 at 11 (SYNG-PQ-01116551).
[157] SYNG-PQ-37240172 at 13 (SYNG-PQ-37240184).

dose of paraquat, almost all of which would be rapidly excreted over several days.[158] Remarkably, even though the purpose of the study was to evaluate the risk of paraquat's neurotoxicity to the brain, Syngenta did not examine the monkey brain tissue for evidence of paraquat residue.

[158] *Ibid.* at 53 (SYNG-PQ-37240224).

G. Syngenta abuses attorney-client privilege to hide the truth about paraquat from the public

1. February 2008 Atlanta Meeting

Syngenta itself acknowledges that it would be inappropriate for lawyers to be advising Syngenta scientists on matters of science and that matters of science should rest with the scientists. *See* Syngenta corporate representative deposition, *Botham Tr. Vol. 2 at 473 lines 8-9*. Yet Syngenta allowed an outside lawyer named Jeffrey Wolff to be intimately involved in decisions and processes deciding how science and scientific matters would be presented from at least early 2008.

Mr. Wolff attended and participated in a Syngenta scientific review meeting in Atlanta, Georgia in February 2008, which was a meeting to present Syngenta's research of paraquat and Parkinson's disease. The presentation included Dr. Marks's paraquat/Charles River black mouse research. Syngenta's in-house counsel, Jonathan Sullivan, made a presentation on "overall governance framework," and Mr. Wolff made a half-hour presentation on "attorney client privilege and communications management."

SYNG-PQT-ATR-16995053

Draft – Jan. 25, 2008
Syngenta Confidential - Attorney Client Privileged

Agenda for the PQ Scientific Review Meeting
Westin Peachtree Plaza Hotel, Tower Room, Atlanta, Georgia

Participants:

Syngenta R&D: Lewis Smith, Janis McFarland, Martin Wilks, Dave Berry, Phil Botham, Nick Sturgess, Kim Travis, Charles Breckenridge
Syngenta Legal: Jonathan Sullivan, Beth Quarles Alan Nadel
Syngenta Public Relations: Sherry Ford. Basel Representative TBD
Outside Counsel: Jeff Wolff, Fulbright & Jaworski
Outside Experts: Jim Simpkins, Jack Mandel, Phil Cole

February 13-14		
Opening Time tbd		
15 min.	Welcome, meeting objectives and principles	L Smith
15 min.	Discussion of overall governance framework	JD Sullivan
30 min.	Presentation on attorney client privilege and communications management */to include discussion on document preservation, and meeting ground rules relating to minutes and notes/*	J Wolff
[ ]	PQ overview – its discovery, properties, uses and toxicity	L Smith
[ ]	Review of biological plausibility of potential association	C Breckenridge
[ ]	Overview of published literature and discussion of external and internal studies experiments	C Breckenridge
[ ]	Discussion of critical technical issues that need to be addressed	L Smith
[ ]	Discussion of methods to address open issues and development of proposed plan for short and long term activities	Phil Botham Martin Wilks
[ ]	Discussion of resources and next steps to develop and execute R&D plan	tbd
[ ]	Regulatory considerations both short and long term	J McFarland
30 min.	Discussion of Public Affairs' considerations and next steps	S Ford
30 min.	Wrap-up and Close	L Smith Legal

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQT-ATR-16995053

It appears that the point of including the lawyers at this meeting was to remind Syngenta scientists to keep their communications secret under the ruse of privileged attorney-client communications. And the point of "communications management" was a reminder that the transmission of any meeting notes or minutes should pass strictly through the lawyers so they could be claimed to be attorney-client privileged communications or work product. Apparently, Mr. Wolff told the scientists at that meeting that if they sent emails only to the lawyers—as opposed to merely copying the lawyers on their communications—then those communications would be privileged documents. *See* "Action Notes" (next page). He further instructed the scientists to label their study work as "work product" and "attorney/client privileged." He also told the scientists that if an outside lawyer like him requested work by the scientists, then that would have a higher level of privilege than if an in-house Syngenta lawyer requested the work.

The primary and perhaps only reason to produce scientific studies in which the work of scientists is labeled as "work product" or "attorney/client privileged" is to ensure that public release of the studies and associated materials is controlled by corporate attorneys; the studies become instruments of public relations and advocacy. This approach is antithetical to scientific enterprise as we know it, in which the results of studies are available for others to critique and build on the original ones. The hiding of unwanted scientific studies or communications between scientists was a strategy used extensively by the tobacco industry and other producers of deadly products. It is shocking to see this strategy used as late as 2008, given the association of this strategy with the tobacco industry.

It is notable that two of the product defense scientists who are listed as participants at this meeting, Jack Mandel of Exponent and Phil Cole, of the University of Alabama Birmingham, later produced and published a review of the literature on paraquat, entitled "Paraquat and Parkinson's disease: An overview of the epidemiology and a review of two recent studies" which reached the predictable conclusion that there is too much uncertainty to determine if there is a relationship between and paraquat exposure and Parkinson's Disease.

502(d)-022360.0001

CONFIDENTIAL AND ATTORNEY CLIENT PRIVILEGED COMMUNICATION

ACTION NOTES FROM ATLANTA MEETING 13-14 FEBRUARY 2008

Attendees:

Dr J L Smith (Chair)	Dr J McFarland
Dr MF Wilks	Dr C Breckenridge
Mr DJ Berry	Dr PA Botham
Dr N Sturgess	Dr K Travis
Dr P Hertle (13th only)	Mr J Sullivan
Ms B Quarles	Mr A Nadel
Ms S Ford	Dr G Diriwaechter
Mr J Wolff (outside Counsel)	

Agenda:

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Governance
Need BO presentation

Attorney Client Privilege
Presentation reqd.

General house keeping rules

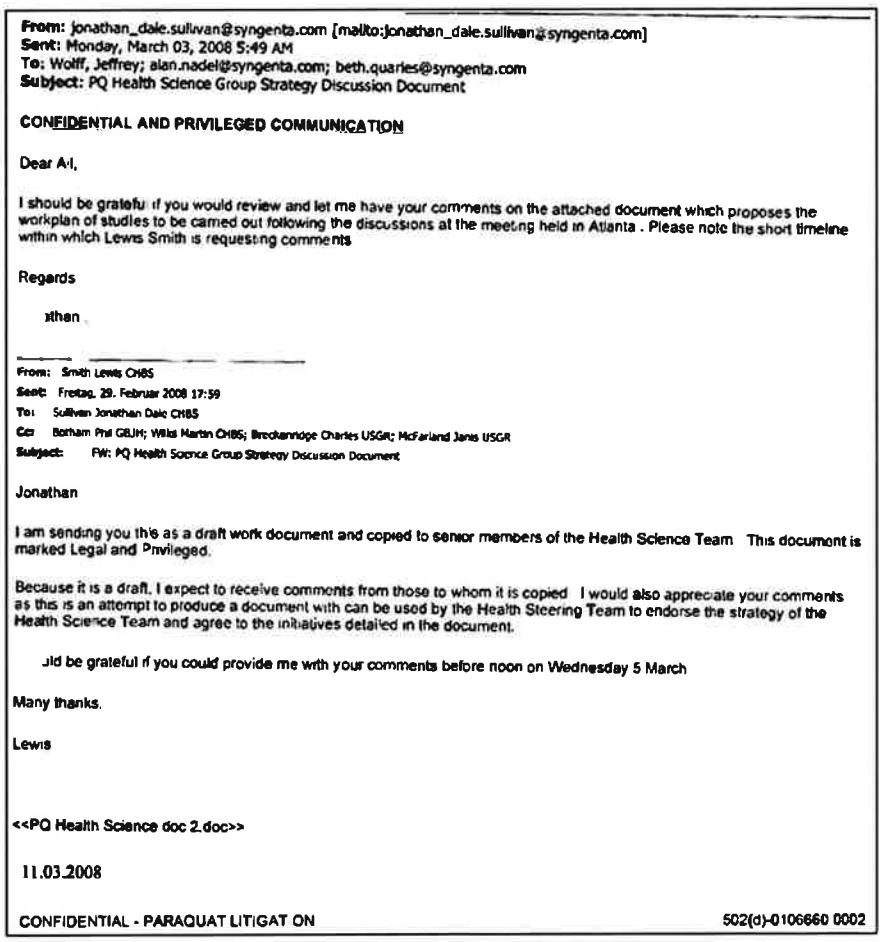
- Attorney Client Privilege applies to legal advice Correspondence on business strategy is nos privileged
- Internal communications with internal or external counsel should make it clear that the correspondence is privileged and that it is for potential paraquat PD litigation.
- Correspondence must be factual – avoid expressing opinions
- Study work should be labelled Work Product Doctrine Material Confidential, and carry the Attorney Client Privilege statement
- Information "cc'd" to external Counsel is not privileged
- Care should be taken on wider circulation of privileged information authored by internal/ external counsel
- Work requested by external counsel has a higher level of privilege than if ordered by Syngenta
- Staff should create separate files (hard copy and electronic) for privileged documents –
  ACTION: JW/AN/DJB/CB to issue clear instructions on files and documentation – to include practices for management of draft documents and slides (eg Sharepoint Teamspace)

CONFIDENTIAL - PARAQUAT LITIGATION 502(d)-022360.0001

2. March 2008 PQ Health Science Group Strategy Discussion

Before the month was out, a document titled "Paraquat Health Science Group Strategy Discussion Document" was being circulated within the company as a result of the discussions at the Atlanta meeting. The document consisted of a scientific proposal of a workplan of studies to be carried out addressing the link between paraquat and Parkinson's disease. And consistent with Mr. Wolff's instructions, the document was being routed through the lawyers rather than being shared among the scientists directly, even though it was a scientific discussion, not a legal one. The primary purpose, if not the only purpose, for having a scientific document like this routed through lawyers, was an attempt to protect it as privileged consistent with Wolff's Atlanta presentation.

502(d)-0106660.0001 (email re Paraquat Health Science Group Strategy Discussion Document)



From: jonathan_dale.sullivan@syngenta.com [mailto:jonathan_dale.sullivan@syngenta.com]
Sent: Monday, March 03, 2008 5:49 AM
To: Wolff, Jeffrey; alan.nadel@syngenta.com; beth.quaries@syngenta.com
Subject: PQ Health Science Group Strategy Discussion Document

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Dear All,

I should be grateful if you would review and let me have your comments on the attached document which proposes the workplan of studies to be carried out following the discussions at the meeting held in Atlanta . Please note the short timeline within which Lewis Smith is requesting comments

Regards

Jthan

From: Smith Lewis CHBS
Sent: Freitag, 29. Februar 2008 17:59
To: Sullivan Jonathan Dale CHBS
Cc: Botham Phil GBJH; Wilks Martin CHBS; Breckenridge Charles USGR; McFarland Janis USGR
Subject: FW: PQ Health Science Group Strategy Discussion Document

Jonathan

I am sending you this as a draft work document and copied to senior members of the Health Science Team This document is marked Legal and Privileged.

Because it is a draft, I expect to receive comments from those to whom it is copied I would also appreciate your comments as this is an attempt to produce a document with can be used by the Health Steering Team to endorse the strategy of the Health Science Team and agree to the initiatives detailed in the document.

uld be grateful if you could provide me with your comments before noon on Wednesday 5 March

Many thanks.

Lewis

<<PQ Health Science doc 2.doc>>

11.03.2008

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And in fact, this is what was attempted with the "Paraquat Health Science Group Strategy Discussion." Consistent with Wolff's instructions at the Atlanta meeting, Syngenta scientists and in-house attorneys were trying to make these scientific documents privileged by claiming they were prepared at the request of lawyers in anticipation of litigation. Even though Mr. Wolff himself did not believe such a claim would survive a challenge for this particular document, it suggests that Wolff's instructions at the Atlanta meeting were understood by the scientists to be extremely broad

in terms of protecting a wide swath of internal documents and communications. Also, although Mr. Sullivan instructed in his email that the privilege markers should be removed from the document. Despite Wolff's advice, Syngenta continued to mark this document privileged.

502(d)-0106660.0001 (email re Paraquat Health Science Group Strategy Discussion Document)

PQ Health Science Group Strategy Discussion Document Page 1 of 2

Zumbiehl Janine CHBS

From: Sullivan Jonathan Dale CHBS
Sent: Dienstag, 4. Marz 2008 18:19
To: Smith Lewis CHBS
Subject: PQ Health Science Group Strategy Discussion Document
Attachments: PQ Health Science Group Strategy - Discussion Document 3-3-08 (2).DOC

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Lewis,

I asked Jeff Wolff together with Alan Nadel and Beth Quarles to review this document and I enclose a message from Jeff Wolff to which is attached a redlined version of the document proposing a number of amendments and raising some questions . A key point is Jeff's conclusion that it would be an artificial construct, and unlikely to survive challenge, to propose that the studies (and by inference the workplan) are being prepared at the request of lawyers in anticipation of litigation and accordingly we must work on the assumption that none of this material will be privileged . The privilege markers should therefore be removed from the document .
I have no additional comments on the content of the document .

ards,

Jonathan .

From: Wolff, Jeffrey [mailto:jwolff@fulbright.com]
Sent: Dienstag, 4. März 2008 01:33
To: Sullivan Jonathan Dale CHBS; Nadel Alan USGR; Quarles Beth USGR
Subject: RE: PQ Health Science Group Strategy Discussion Document

Jonathan:

Since I am unsure if I will have the opportunity to discuss the PQ Health Science workplan with Alan before my meetings in the morning and in view of the short timeline for comments requested by Lewis Smith, I am taking the liberty of forwarding my attached redlined comments directly to you.

not believe it is realistic that we will be successful in characterizing this workplan or the studies as protected by the work product privilege in that we will be hard pressed to offer proof that the studies were prepared at the request of lawyers in anticipation of litigation.

Accordingly I have made suggested revisions to the text which are directed at improving it in the event it falls into the hands of adversaries. I have also raised a questions about and challenges to certain statements in the document.

Regards.

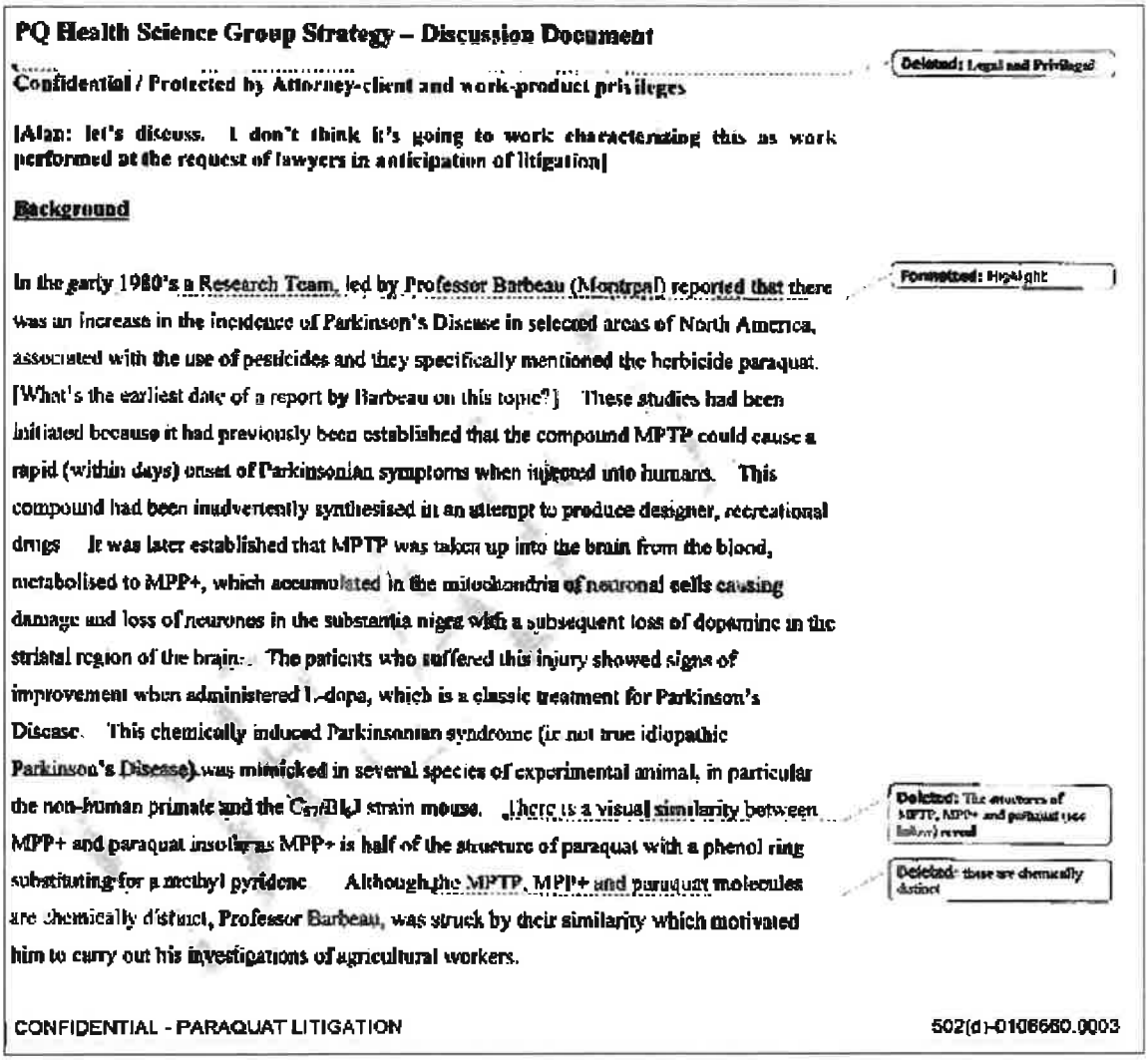
Jeff

Jeffrey S. Wolff
Fulbright & Jaworski
1301 McKinney
Suite 5100
Houston, TX 77010-3095
Phone: 713-651-5466

11.03.2008

CONFIDENTIAL - PARAQUAT LITIGATION 502(d)-0106660.0001

502(d)-0106660.0001 (Paraquat Health Science Group Strategy Discussion Document)



PQ Health Science Group Strategy – Discussion Document

Deleted: Legal and Privileged

Confidential / Protected by Attorney-client and work-product privileges

[Alan: let's discuss. I don't think it's going to work characterizing this as work performed at the request of lawyers in anticipation of litigation]

Background

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In the early 1980's a Research Team, led by Professor Barbeau (Montreal) reported that there was an increase in the incidence of Parkinson's Disease in selected areas of North America, associated with the use of pesticides and they specifically mentioned the herbicide paraquat. [What's the earliest date of a report by Barbeau on this topic?] These studies had been initiated because it had previously been established that the compound MPTP could cause a rapid (within days) onset of Parkinsonian symptoms when injected into humans. This compound had been inadvertently synthesised in an attempt to produce designer, recreational drugs. It was later established that MPTP was taken up into the brain from the blood, metabolised to MPP+, which accumulated in the mitochondria of neuronal cells causing damage and loss of neurones in the substantia nigra with a subsequent loss of dopamine in the striatal region of the brain. The patients who suffered this injury showed signs of improvement when administered L-dopa, which is a classic treatment for Parkinson's Disease. This chemically induced Parkinsonian syndrome (ie not true idiopathic Parkinson's Disease) was mimicked in several species of experimental animal, in particular the non-human primate and the C57BL/J strain mouse. There is a visual similarity between MPP+ and paraquat insofar as MPP+ is half of the structure of paraquat with a phenol ring substituting for a methyl pyridene. Although the MPTP, MPP+ and paraquat molecules are chemically distinct, Professor Barbeau, was struck by their similarity which motivated him to carry out his investigations of agricultural workers.

Deleted: The structures of MPTP, MPP+ and paraquat (see below) reveal

Deleted: these are chemically distinct

CONFIDENTIAL - PARAQUAT LITIGATION

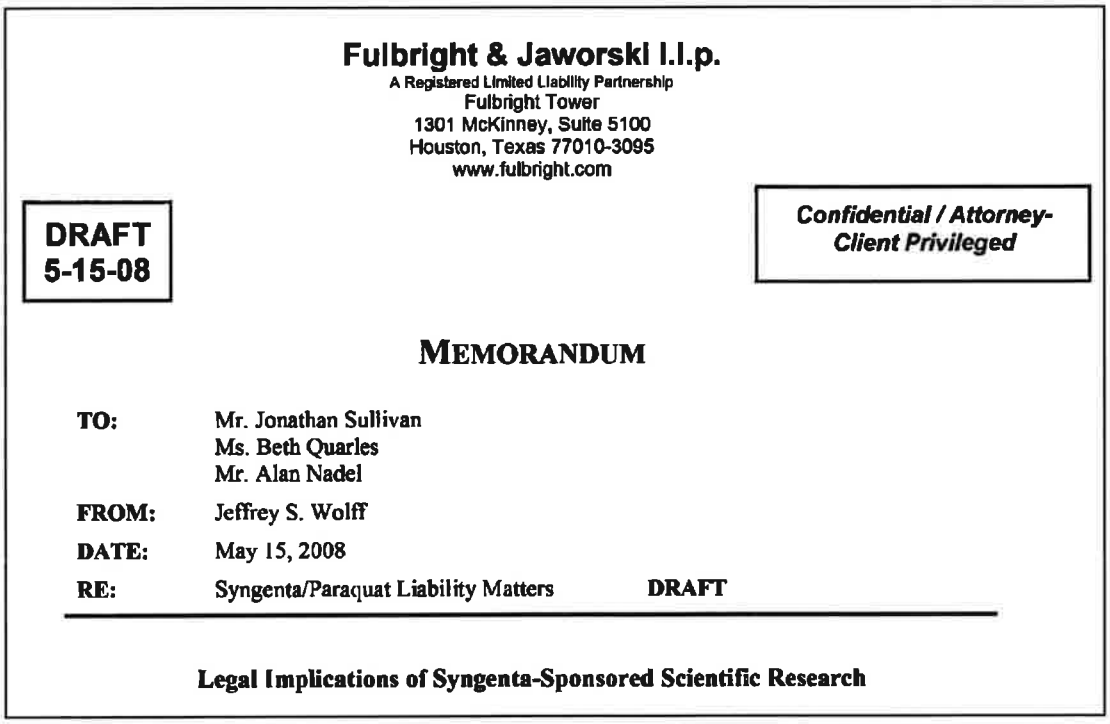
502(d)-0106660.0003

There are many examples of Syngenta attempting to conceal documents by routing them through lawyers. *See, e.g.*, 502(d)-027368.0001; 502(d)-001599.0001 There are still more examples of this (in following sections of this report) that involve more than merely routing through lawyers..

3. Wolff memo May 2008

Mr. Wolff was apparently asked to analyze from a legal perspective whether Syngenta should undertake the scientific research proposed in the Paraquat Health Science Group Strategy Discussion Document, because in May 2008, Mr. Wolff wrote a memorandum addressing the wisdom of such Syngenta-sponsored research. This is interesting because it implies that Syngenta's decision about whether to sponsor such research was not driven solely by scientific or human health considerations.

502(d)-081076.0001 Wolff memo



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1301 McKinney, Suite 5100
Houston, Texas 77010-3095
www.fulbright.com

DRAFT 5-15-08

Confidential / Attorney-Client Privileged

MEMORANDUM

TO: Mr. Jonathan Sullivan
Ms. Beth Quarles
Mr. Alan Nadel

FROM: Jeffrey S. Wolff

DATE: May 15, 2008

RE: Syngenta/Paraquat Liability Matters **DRAFT**

Legal Implications of Syngenta-Sponsored Scientific Research

Notably, in the very last sentence of his memorandum, Mr. Wolff refers to "the widely-recognized void" in the existing paraquat-Parkinson's research in May 2008. But having attended Syngenta's Atlanta meeting just three months earlier, Mr. Wolff would have been aware of Dr. Sturgess's presentations of Dr. Marks's work with paraquat and the Charles River black mouse. He would have been aware that Dr. Marks had duplicated the results of the Cory-Schlecta and Di Monte groups' work. So, Mr. Wolff knew there was no "void" in the research. The only void was research that did *not* implicate paraquat's role in causing Parkinson's disease. Filling a "void" of research favorable to the continued widespread use of paraquat as a herbicide appears to be the void Mr. Wolff thought needed to be filled. This is an example of Syngenta diluting, polluting and confusing the existing science that linked paraquat and Parkinson's disease.

6. **Conclusion**

The risks of harm to Syngenta associated with the failure to initiate scientific inquiry into the paraquat/Parkinson's disease causation issues discussed in this memorandum materially outweigh the possible hazards of sponsoring this research. The factors compelling this conclusion include Syngenta's global leadership position in the paraquat business, its public

[illegible] Nov 2007 Syngenta Code of Conduct at p. 9 ("Syngenta respects the academic freedom and tradition of its partners and the need of its scientists to publish results.")

[illegible] - 12 -

CONFIDENTIAL - PARAQUAT LITIGATION 502(d)-081078-0012

DOCUMENT SUBJECT TO 502(D)

Mr. Jonathan Sullivan
Ms. Beth Quarles
Mr. Alan Nadel
May 14, 2008

commitment to high standards of product stewardship and its unique insights to proposed research which are aimed at advancing the state of scientific knowledge on key causation-related issues. There is a widely-recognized void in the existing research and Syngenta is especially qualified to help fill it

And in fact, review of the entire memo makes clear that Wolff was proposing Syngenta should "fill" the "void" with research aimed at defending paraquat. He was not proposing that Syngenta scientists conduct research to determine *whether* there was any causal link between paraquat and Parkinson's disease but rather "that there is no evidence that paraquat exposure causes Parkinson's disease."

Mr. Wolff also acknowledged under that heading that Syngenta's "research objectives are distinguishable from other researchers."

b. Syngenta is in a unique position to initiate research directed at demonstrating that there is no evidence that paraquat exposure causes Parkinson's disease.

Syngenta's research objectives are distinguishable from other researchers for several reasons.

First, he notes that *only* Syngenta has a motive "to design research studies aimed at defending the safety of the product."

> First, no other researcher has Syngenta's motivation to design research studies aimed at defending the safety of the product. Too often, researchers and recipients of research grants are motivated to implicate substances rather than defend them. Syngenta has the flexibility to focus its sponsorship of causation-related research that is more narrowly directed at causation issues as compared to broad-scale studies underway such as the Agricultural Health Study.[16]

So here we have the lawyer proposing that Syngenta design its studies with the objective of *defending* paraquat—a predetermined outcome in favor of the safety of using paraquat. Mr. Wolff also writes that "other researchers" are "too often ... motivated to implicate substances rather than defend them," apparently as further justification of research designed with the aim of "defending the safety" of paraquat.

Wolff also seems to hope that Syngenta's epidemiological studies would find a lot of other causes of Parkinson's disease, exactly like the industry approach to epidemiological evidence I discuss earlier in this report. In particular, Wolff urges compilation of "a comprehensive list of risk factors for Parkinson's disease" in an attempt to shift the blame to other possible causes of Parkinson's disease.

> Third, Syngenta-sponsored research, particularly the epidemiological studies, may be unique in their objective to identify a comprehensive list of risk factors for Parkinson's disease. It is not clear that existing epidemiological studies have properly accounted for all such risk factors.

Wolff also advised that the lawyers' involvement in research should be concealed: "The names of legal counsel should not appear in the distribution list of written communications with retained researchers. Notably, Mr. Wolff did not say the lawyers should not be involved in the scientific research but only that their names should not show up in the communications. And to that end, Wolff recommended that a member of the Syngenta research team make sure that Syngenta's lawyers were "copied on and updated about all communications with researchers."

> **f. Evidence of legal counsel's appearance or participation in communications with the retained researchers should be minimized.**
>
> The names of legal counsel should not appear in the distribution list of written communications with retained researchers. Similarly, counsel's presence in meetings or phone conferences with researchers should not be prominently featured. Counsel for adversaries often seek to draw sinister inferences from any role of counsel in scientific endeavors and they will use such evidence to argue that the research is being manipulated by lawyers.
>
> Consideration should be given to having a designated member of the Syngenta research team charged with making sure that Syngenta counsel are copied on and updated about all communications with the researchers.

4. Additional examples of Wolff editing internal documents

In a July 2008 document (see below), Mr. Wolff comments on and suggests edits to the notes of a joint meeting of the Product Safety Global Product Registration teams. A few months earlier, the Paraquat Issue Leadership Team (PILT) had decided that Product Safety should "consider risk assessment in relation to operator exposure," i.e., farmers or farm workers. (*Quoting Sullivan email at page 1.*) The Issue Leadership Team decided this risk assessment "should be carried out by Product Safety in accordance with their regulatory duty of care." (*Quoting Sullivan*). According to the draft notes of the July 10 meeting, the Product Safety and Global Product Registration teams found:

- "The one consistent finding in animal studies is the loss of dopaminergic neurones in the substantia nigra pars compacta of male C57BL6J mice."
- "This finding is judged to be real, to be related to paraquat treatment, and to be adverse in nature."
- "In the absence of evidence to the contrary, it is prudent to assume that this finding is also potentially qualitatively relevant to man."

502(d)-0107074.0001

Zumbiehl Janine CHBS

From: Sullivan Jonathan Dale CHBS
Sent: Dienstag, 15. Juli 2008 10:01
To: jwolff@fulbright.com; Nadel Alan USGR
Cc: Maeder Christoph CHBS
Subject: PARAQUAT
Attachments: draft notes.doc; 080619 draft minutes.doc

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Jeff and Alan,

I attach for your review and comments two sets of draft Minutes or Notes of internal meetings relating to paraquat, including draft enclosures, which I received yesterday.

The first set of draft Minutes records a Meeting of the "Inteon" Science and Regulatory Team held on 19 June to review the sequence of disclosure meetings held in April and May with applicable regulatory authorities and to consider the study program associated with future formulation strategy. In the latter area the Minutes appear to evince an interest in changing, in relation to new formulations, the approach to testing for acute oral toxicity and to suggest that only rat and not dog studies would be carried out. In addition a question is raised as to the minimum level of testing which would be required from a regulatory perspective to demonstrate that a new formulation is of equivalent safety to "Inteon".

The second document is a set of draft Notes of a joint meeting of the Product Safety and Global Product Regulation teams held to consider the risk assessment in relation to operator exposure, based on the published experimental studies, which it was agreed by the Issue Leadership Team on 16 April 2008 should be carried out by Product Safety in accordance with their regulatory duty of care.

The risk assessment is at least for me as a non-scientist quite difficult to follow and I have put in a call to John Doe with a view to having him explain it to me. The conclusion appears to be that the predicted NOEL for neuronal cell loss in humans which can be extrapolated from the mouse studies is about 50 times higher than the current regulatory reference dose of 0.0005 mg/kg/d. However it is accepted that there is significant uncertainty around these predictions which could only be resolved through further studies. There are a number of statements in the paper which taken out of context would potentially be unhelpful.

Jonathan.

16.07.2008

Phil Botham
Angela Brady
Andy Cook
Roland Dieterle
John Doe
Kersten Mewes

10th July 2008

Draft notes from PS/GPR meeting
On 10th July 2008

1. Assessment of the operator exposure reference dose in light of emerging data

The following draft Product Safety evaluation of the reference dose was reviewed.

Draft PQ Parkinsons
Draft Reference Dose

Clarifications of specific points during the discussion lead to the following executive summary which will be included in the next version of the PS document.

- The one consistent finding in animal studies is the loss of dopaminergic neurones in the substantia nigra C57BL6J mice.
- This finding is judged to be real, to be related to treatment and to be adverse in nature
- In the absence of evidence to the contrary, it is prudent to assume that this finding is potentially qualitatively relevant to man
- The ip dose route is not a relevant route of exposure and therefore requires route-to-route extrapolation
- Nevertheless, we should check whether these findings would change the reference dose for operators
- In absence of data from a study of appropriate type and duration, we should try to estimate a reference dose using a number of assumptions, each with associated uncertainty
- Although the estimated reference dose is approximately 2-fold lower than the current Syngenta reference dose position, given the uncertainty of the calculation Product Safety considers the difference not to be significant
- 2007 have independently concluded using a PBPK model that there is likely to be a substantial margin of safety for operators via the dermal route
- The robustness of the conclusions from both Product Safety and McIntosh & Kedderis would benefit from the generation of more relevant data to remove some of the levels of uncertainty. These data should still be generated in the C57Bl6 mouse in the absence of evidence regarding relevance to man of effects seen in this strain, which should also be investigated
- Given the big margins of safety for dietary exposure, there are no concerns for safety to consumers
- There is no evidence that the foetus is more susceptible to this effect.

In his comments on the draft notes, Mr. Wolff finds the first bulleted statement regarding "loss of dopaminergic neurons" to be "unhelpful." He also wants language in the second and third bullets removed (the phrase "adverse in nature" in the second, and the language regarding the relevance to humans in the third).

SYNG-PQ-31451013

-----Original Message-----
From: Wolff, Jeffrey [mailto:jwolff@fulbright.com]
Sent: Mittwoch, 16. Juli 2008 18:44
To: Sullivan Jonathan Dale CHBS
Cc: Nadel Alan USGR
Subject: RE: Comments on PQ team meeting minutes 7-15-08

Jonathan:

Angela Brady's answers to the questions I raised in both documents were very helpful and appreciated. With respect to the problematic language in the reference dose report which reads as follows:

"The one consistent finding from the body of animal studies is the loss of dopaminergic neurones in the substantia nigra pars compacta of male C57Bl6J mice. This finding is judged to be real, to be related to paraquat treatment, and to be adverse in nature."

I would suggest removing the text: "and to be adverse in nature" so that the last sentence reads "This finding is judged to be real and related to paraquat treatment."

Angela addressed all my other comments to the draft notes from PS/GPR meeting.

With respect to the draft minutes of the Inteon Science and Regulatory Team Meeting, I concur with each of Angel's proposed revisions of text I had flagged in redlined comments to these minutes.

Regards.

Jeff

-----Original Message-----
From: jonathan_dale.sullivan@syngenta.com
[mailto:jonathan_dale.sullivan@syngenta.com]
Sent: Wednesday, July 16, 2008 10:58 AM
To: Wolff, Jeffrey
Cc: alan.nadel@syngenta.com
Subject: Comments on PQ team meeting minutes 7-15-08

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

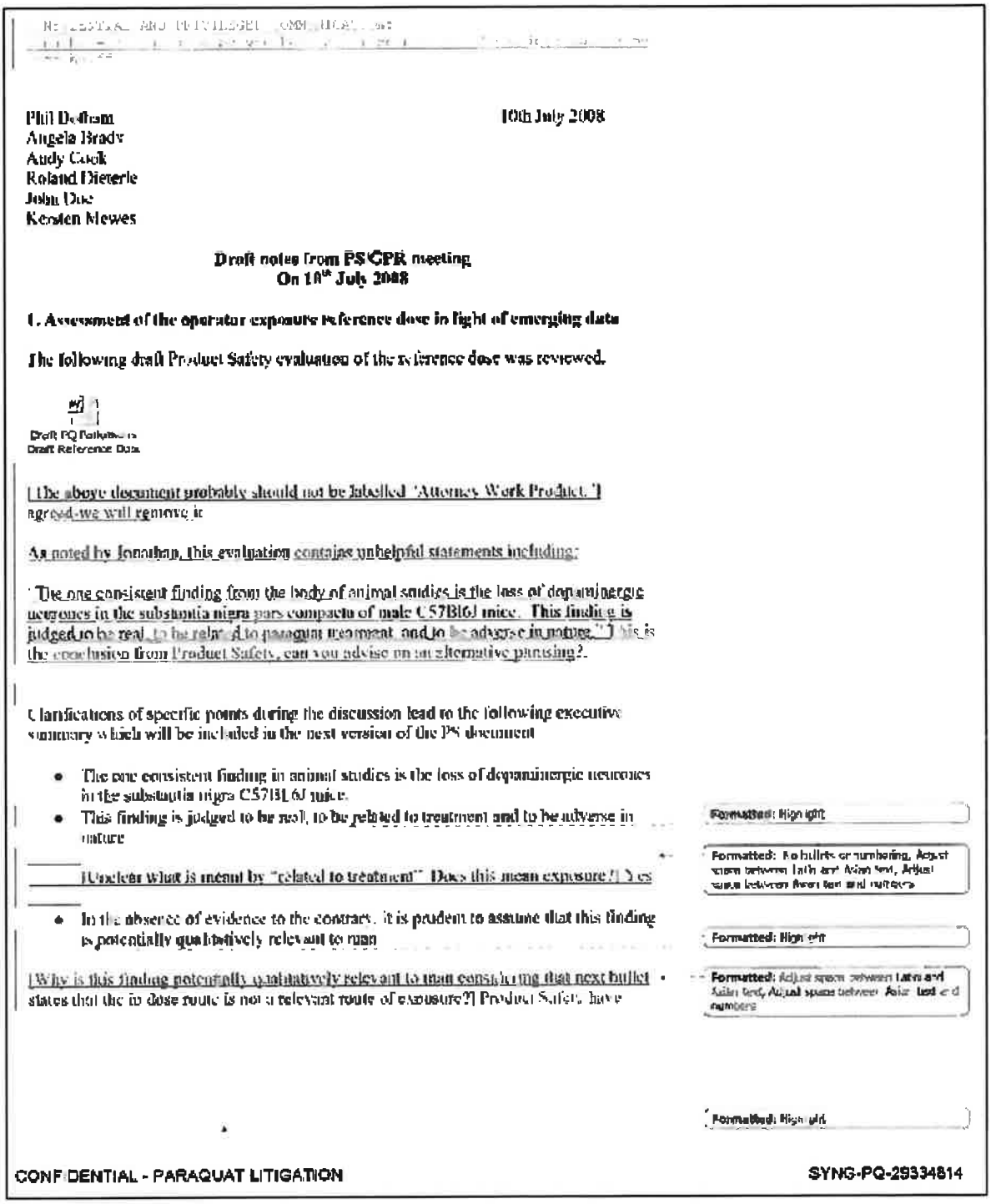
Jeff,

Attached are Angela Brady's responses to your comments including some proposals for amendments . I should be grateful if you would review these responses and advise on the

2

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQ-31451014

SYNG-PQ-29334814



Phil Dedham
Angela Brady
Andy Cook
Roland Dieterle
John Doe
Kersten Mewes

10th July 2008

Draft notes from PS/CPR meeting
On 10th July 2008

1. Assessment of the operator exposure reference dose in light of emerging data

The following draft Product Safety evaluation of the reference dose was reviewed.

Draft PQ Reference Dose

[The above document probably should not be labelled 'Attorney Work Product.']
agreed-we will remove it

As noted by Jonathan, this evaluation contains unhelpful statements including:

'The one consistent finding from the body of animal studies is the loss of dopaminergic neurones in the substantia nigra pars compacta of male C57Bl6J mice. This finding is judged to be real, to be related to paraquat treatment, and to be adverse in nature.'] his is the conclusion from Product Safety, can you advise on an alternative phrasing?.

Clarifications of specific points during the discussion lead to the following executive summary which will be included in the next version of the PS document

- The one consistent finding in animal studies is the loss of dopaminergic neurones in the substantia nigra C57Bl6J mice.
- This finding is judged to be real, to be related to treatment and to be adverse in nature

[Unclear what is meant by "related to treatment". Does this mean exposure?] Yes

- In the absence of evidence to the contrary, it is prudent to assume that this finding is potentially qualitatively relevant to man

[Why is this finding potentially qualitatively relevant to man considering that next bullet states that the iv dose route is not a relevant route of exposure?] Product Safety have

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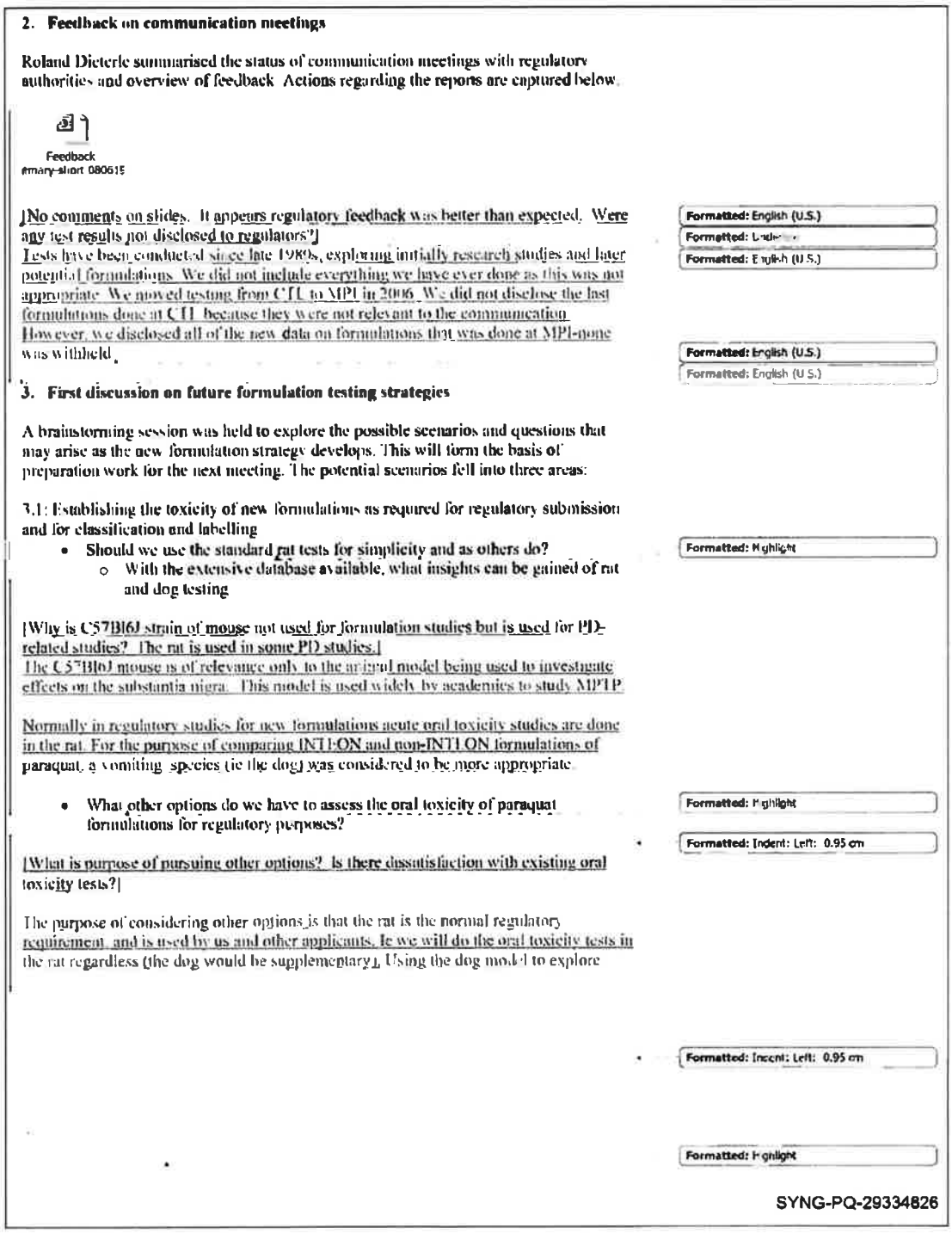
SYNG-PQ-29334814

See also SYNG-PQ-29673328 (part of related email confirming that Wolff's change was accepted); **SYNG-PQ-31451013**.

Below are additional examples Wolff's editing of internal Syngenta documents.

SYNG-PQ-29334825 (June 2008 Inteon Science and Regulatory Team Meeting minutes)



2. Feedback on communication meetings

Roland Dieterle summarised the status of communication meetings with regulatory authorities and overview of feedback. Actions regarding the reports are captured below.

Feedback
#mary-short 080615

[No comments on slides. It appears regulatory feedback was better than expected. Were any test results not disclosed to regulators?]
Tests have been conducted since late 1980s, exploring initially research studies and later potential formulations. We did not include everything we have ever done as this was not appropriate. We moved testing from CTL to MPI in 2006. We did not disclose the last formulations done at CTL because they were not relevant to the communication.
However, we disclosed all of the new data on formulations that was done at MPI-none was withheld.

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3. First discussion on future formulation testing strategies

A brainstorming session was held to explore the possible scenarios and questions that may arise as the new formulation strategy develops. This will form the basis of preparation work for the next meeting. The potential scenarios fell into three areas:

3.1: Establishing the toxicity of new formulations as required for regulatory submission and for classification and labelling

- Should we use the standard rat tests for simplicity and as others do?
  - With the extensive database available, what insights can be gained of rat and dog testing

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[Why is C57Bl6J strain of mouse not used for formulation studies but is used for PD-related studies? The rat is used in some PD studies.]
The C57Bl6J mouse is of relevance only to the animal model being used to investigate effects on the substantia nigra. This model is used widely by academics to study MPTP.

Normally in regulatory studies for new formulations acute oral toxicity studies are done in the rat. For the purpose of comparing INTI-ON and non-INTI ON formulations of paraquat, a vomiting species (ie the dog) was considered to be more appropriate.

- What other options do we have to assess the oral toxicity of paraquat formulations for regulatory purposes?

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[What is purpose of pursuing other options? Is there dissatisfaction with existing oral toxicity tests?]

The purpose of considering other options is that the rat is the normal regulatory requirement, and is used by us and other applicants. Ie we will do the oral toxicity tests in the rat regardless (the dog would be supplementary). Using the dog model to explore

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SYNG-PQ-29334826

502(d)-002439.0001 Syngenta Standby Statement on Paraquat

DRAFT

Syngenta Standby Statement on Paraquat and its Relationship to Parkinson's Disease

[Jeff Wolff comments highlighted in yellow 6 28-08]

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Background

Parkinson's disease (PD) is a neurodegenerative disorder and one of the most common neurological diseases affecting humans. PD results from particular defects in a specific part of the brain called the *substantia nigra*, involving the loss of specific neurones. The prevalence of PD increases with age, and there has been a significant level of scientific interest in the factors which could cause the disease. [Consider footnoting literature support that can be provided to medical case support is requested for such statements]

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Epidemiological studies have suggested that both genetic and environmental factors are involved in the development of PD. However, the relative contribution of these and the identification of any environmental factors is still the subject of considerable debate within the scientific community. A number of studies have provided varying degrees of evidence that certain environmental factors, among them living in a rural environment, farming activities, well water drinking; metals; animal fat consumption; infection and head injury could increase the risk of developing PD in humans. Other factors like smoking and caffeine intake could decrease it, based on these studies.

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Claims have also been made of the increased occurrence of PD being associated with pesticide use. A number of recent publications using experimental models have raised the possibility of an association of several pesticides (including paraquat and the fungicide, maneb) with PD. Paraquat was examined based on the compound's apparent structural similarity to the compound MPTP and its toxic metabolite MPP+, which were shown to cause Parkinsonian symptoms in young drug addicts in the 1980s.

[Consider need for brief background statement on Paraquat]

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Paraquat is an active ingredient used in Crop Protection products (sometimes called pesticides). Paraquat protects crops by controlling a wide range of weeds that reduce both crop yield and quality by competing with the crop for water, nutrients, and light. Paraquat is one of the most widely used herbicides in the world and is used to control weeds in a wide variety of crops. The key characteristics that distinguish the rapid-acting contact herbicide paraquat from other active ingredients used in plant protection products are: Paraquat is non-selective, which means it kills a wide range of annual grass and broad-leaved weeds and the tops of established perennial weeds. Paraquat is very fast acting. Paraquat is rain fast within minutes of application. Paraquat becomes biologically inactive upon contact with soil. When used in accordance with manufacturers' recommendations, paraquat can deliver safe, effective weed control, generating social and economic benefits while protecting the land for future generations.

[Source: edited version of statement which appears at www.paraquat.com]

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Syngenta Position

Paraquat is and will continue to be vital to meet the increasing global demand for food, fiber and fuel from agriculture, and is one of the world's most effective and most environmentally benefic al herbicides with an important role to play in increasing agricultural productivity. It is also one of the most extensively researched products ever, registered in over 100 countries

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5. Guidelines for recording paraquat meeting minutes

A few months later, in October 2008, Syngenta issued guidelines for paraquat-related meetings prepared by Mr. Wolff. The Guidelines provided special instructions for any paraquat-related meetings at which a lawyer spoke. Specifically, minute-takers were instructed twice to confer with a Syngenta lawyer before completing minutes of a paraquat meeting at which a lawyer spoke. In November 2008, the guidelines issued to a broader audience within the company, and they were reissued in May 2011.

SYNG-PQ-05039003

From: Cook Andy GBJH
Sent: Tuesday, November 04, 2008 10:33 AM
To: Breckenridge Charles USGR; Sturgess Nick GBJH; Travis Kim GBJH; Mewes Kersten CHBS; Botham Phil GBJH; Wilks Martin CHBS; McFarland Janis USGR; Hertl Peter CHBS
Cc: Berry Dave (ext) GBJH; Smith Lewis GBAP
Subject: Meeting Minutes Guidelines.pdf - Adobe Reader
Attachments: 10-23-08 Meeting Minutes Guidelines.pdf

Dear all,

Our legal advisors have recently provided the attached useful guidance for us. I have cleared the wider distribution of this guidance to the team and would appreciate your taking the time to read this in advance of the Atlanta meeting.

I believe this guidance will be helpful to all of us in moving forward.

Regards.

Andy

SYNG-PQ-05039003

SYNG-PQ-04984359 Guidelines for Recording Paraquat-Related Meeting Minutes; see also SYNG-PQ-05039004 (the guidelines that were circulated).

8. Confer with a Syngenta lawyer before completing minutes of a meeting at which Syngenta legal counsel spoke to determine whether the discussion is privileged. It may be necessary to prepare a separate summary of legal discussions.

70408513.2 - 1 - October 23, 2008

SYNG-PQ-04984359

9.	Confer with a Syngenta lawyer before completing minutes of a meeting at which Syngenta legal counsel spoke to determine whether a modification to the distribution list of the minutes is in order.

The guidelines were recirculated in 2011.

SYNG-PQ-05038997

From: McFarland James USGR
Sent: Wednesday, May 11, 2011 5:36 PM
To: Reeve Brian USGR; Dixon Monty USGR; Campbell Dan USGR; Malarkey Trish USRE; Hanley Jr Thomas USGR
Subject: FW: PQ Health Science Team - agenda
Attachments: Windsor 26 May 2011 afternoon agenda.docx; Windsor 25-26 May 2011 agenda.docx; Meeting Minutes Guidelines.pdf - Adobe Reader
Sensitivity: Confidential

-----Original Message-----
From: Cook Andy GBJH
Sent: Wednesday, May 11, 2011 11:48 AM
To: Burton Judith (ext) GBJH; Botham Phil GBJH; Sullivan Jonathan Dale CHBS; Smith Lewis GBAP; Breckenridge Charles USGR; Berry Dave (ext) GBJH; Brown Richard Anthony CHBS; Mewes Kersten CHBS; Travis Kim GBJH; Sturgess Nick GBJH; Navarro Lisa CHBS; McFarland James USGR; Campbell Clive CHBS; Minnema Daniel USGR; Hert Peter CHBS; Nadel Alan USGR
Subject: PQ Health Science Team - agenda
Sensitivity: Confidential

Attached are the draft agendas for the May meeting at Savill Court. The first covers the 25th and the morning of 26th, the second is for the Syngenta internal discussion on the afternoon of 26th.

The previous advice from Legal is that we should not distribute the agenda to the external attendees

As a reminder, I also enclose a copy of the advice from Legal for good meeting practice.

Please contact me if you have any proposed additions.

Regards

Andy Cook

Product Safety
Jealotts Hill International Research Centre, Bracknell, Berkshire. RG42 6EY Tel: 44 (0) 1344 414177 Mobile 44 (0) 7876 131232 Fax 44 (0) 1344 416690 andy.cook@syngenta.com

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6. Lawyers and the Widnes study

In late 2008, an internal study was proposed that became known as the Widnes Study. It was to be a study of Parkinson's disease in current and former employees of Syngenta (or its predecessor companies) who worked in the manufacture of paraquat at the former plant at Widnes in the UK. In January 2009, in-house attorney Sullivan circulated a draft paper defining the research question for the Widnes epidemiology study that was to be put to an expert epidemiologist group.

So again, we see scientific papers being routed through lawyers. But beyond that, Mr. Wolff not only reviewed the draft paper defining the research question, but he reviewed it first, before it was sent to any of the other Syngenta scientists on the Widnes team. And as a result of Wolff's review, the document was revised "to address comments made by Jeff Wolff." When Sullivan forwarded the revised draft to a wider audience, he instructed the recipients to respond only to him if they had further comments on the draft.

502(d)-0120535.0001

Message

From: Smith Lewis CHBS [/O=MESSAGING/OU=BE-AG/CN=RECIPIENTS/CN=LEWIS SMITH]
Sent: 1/9/2009 5:15:50 PM
To: Sullivan Jonathan Dale CHBS [/O=MESSAGING/OU=BE-AG/CN=RECIPIENTS/CN=SULLIJO2]
Subject: RE: Widnes Worker Study protocol 12-18-08 - jsw comments v1 is clean (3)

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Jonathan

I agree with the suggested changes to the draft document prepared by Martin Wilks. It is particularly important to caviat the certainty of our knowledge concerning the exposure of the Widnes workers to paraquat and other chemicals. Outside counsel is correct in pointing out that there is limited, qualitative exposure data and certainly no quantitative data.

The principle research question is as we have discussed, although even in agreeing to this it is important to recognise that the expert epidemiologist may have a view as to the structure of the question when they have considered the viable epidemiological approaches that could be used to investigate it.

For my part I do not think a meeting is necessary to meet agreement on this modified document, but obviously Sandra will have the last word.

Hope this helps.

Lewis

502(d)-0120535.0001

SYNG-PQ-29346766 (J. Sullivan instructions to respond only to him (to keep privileged)

Message

From: Smith Lewis CHBS [/O=MESSAGING/OU=RE-AG/CN=RECIPIENTS/CN=LEWIS.SMITH]
Sent: 1/15/2009 5 26.46 PM
To: Sullivan Jonathan Dale CHBS [/O=MESSAGING/OU=BE-AG/CN=RECIPIENTS/CN=SULLIJO2]
Subject: Re: Widnes Worker Study Protocol

Jonathan
I have nothing to add

Lewis

From: Sullivan Jonathan Dale CHBS
To: Smith Lewis CHBS; Doe John GBJH; Aruffo Sandro CHBS; Wolff, Jeffrey ; Nadel Alan USGR
Cc: Wilks Martin CHBS; Campbell Clive CHBS
Sent: Tue Jan 13 14:13:53 2009
Subject: Widnes Worker Study Protocol
CONFIDENTIAL AND PRIVILEGED COMMUNICATION

I enclose for your attention a revised draft of the paper defining the research question which it is proposed would be put to the expert epidemiologist group who would be asked to consider a study on the living population of individuals formerly employed at the 4'4 bipyridyl plant at Widnes .
The revised draft is designed to address comments made by Jeff Wolff, Lewis Smith and Sandro Aruffo on the previous draft, with reference in particular to (1) the distinction between Parkinson's Disease and parkinsonism and (2) our state of knowledge with regard to exposure of the workforce .
Please note that the document is intended to serve as a basis for discussion with the external expert team but would not be provided to members of that team . Only the research question itself would be put to the team .
I should be grateful if you would let me know (responding to me only) as soon as possible whether or not you have any further comments on the revised draft .

Jonathan .

SYNG-PQ-29346766

See also **SYNG-PQ-31434314** (the draft paper defining research Q for Widnes study)

7. Wolff February 2009 memo regarding the Widnes study

Wolff's involvement with the Widnes study continued in February. He counseled in-house attorneys Sullivan and Nadel how to conduct interviews of the employees who were the subjects of the studies to make a claim of attorney-client privilege. The interviews, however, were for the business purposes (*i.e.*, scientific study), not for legal representation.

502(d)-017191.0001

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HOUSTON, TEXAS 77010-3095
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Confidential / Attorney-Client Privileged

MEMORANDUM

TO: Jonathan Sullivan
Alan Nadel

FROM: Jeffrey S. Wolff

DATE: February 17, 2009

RE: Syngenta/Paraquat Liability Matters

Responses to Questions Regarding Widnes Interviews, Scientific Presentations at the Toxicology Forum and Lewis Smith's Employment

Jonathan, the questions raised in your February 13, 2009 email message regarding the Widnes interviews, the proposed scientific presentations at the Toxicology Forum, and Lewis Smith's employment are set out below followed by my responses which appear in the indented text beginning with the word "Comment."

1. Clive Campbell has expressed interest in interviewing a number of individuals (in his conversation with me on the subject he named four) who were employed at the 4'4-bipyridyl plant at Widnes, in order to build up a better picture of the exposure profile in connection with the assessment of the feasibility of carrying out an epidemiological study. What are the pros and cons of taking this step from a litigation perspective and would the position be different if the interviews were conducted by in-house or external counsel in the UK (recognizing that this of itself could be sensitive from the perspective of the interviewees)? The people involved are all current or former employees of Syngenta or its legacy companies.

> Comment: If the interviews are conducted by Dr. Campbell alone, it is highly likely that any information he learns or written interview summaries he prepares would not be protected by either the attorney-client or the work-product privileges. It is also highly likely that any written or verbal communications involving Dr. Campbell concerning the results of the interviews would not be privileged unless such communications were directed by Mr. Campbell to legal counsel seeking legal advice, and then only the communication of the information to counsel would be privileged, not the underlying information obtained by Dr. Campbell without the assistance of counsel. In other words, information that is not

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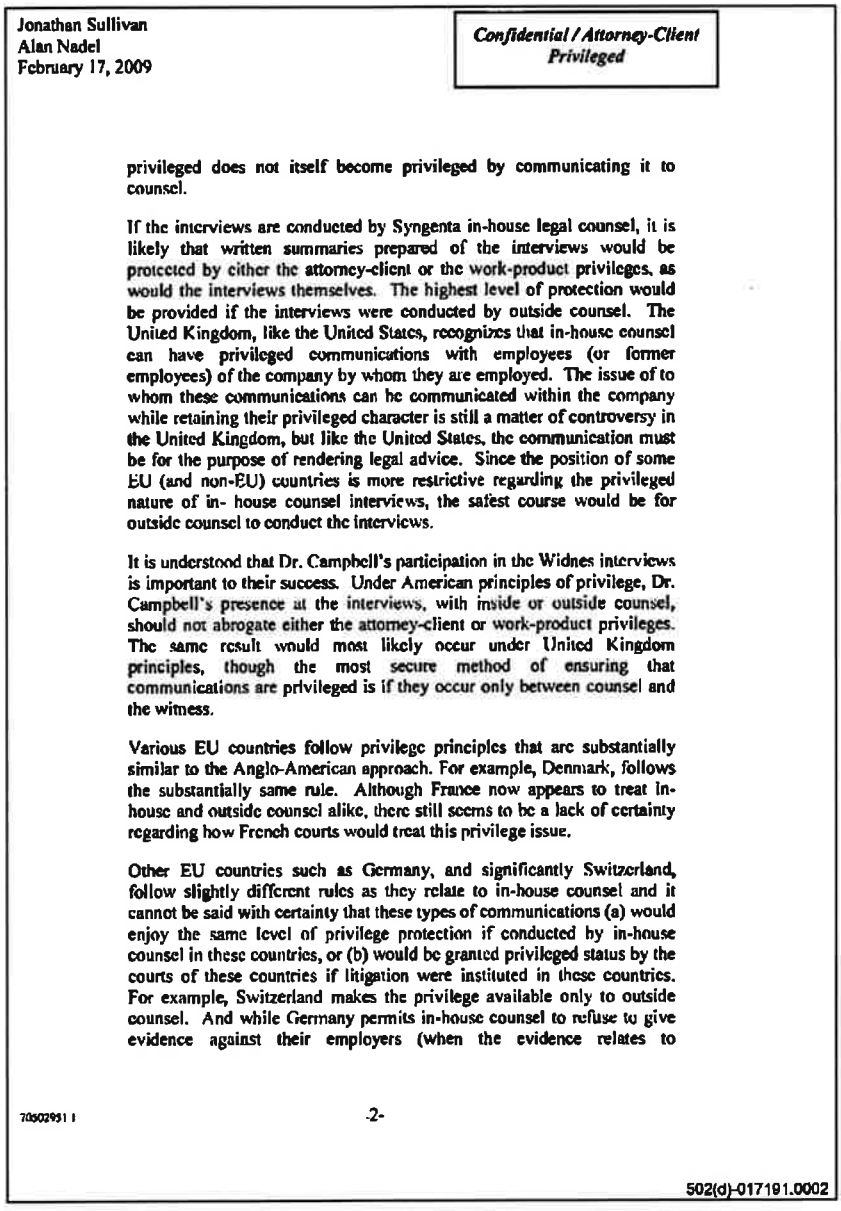
Syngenta's Dr. Clive Campbell had proposed interviewing Widnes workers in order to get a "better picture" of the degree to which they may have been exposed to paraquat while working there. Mr. Wolff suggested that having outside lawyers (like him) conduct the interviews with Dr. Campbell present would be the "safest course"—safest, that is, in terms of keeping the interviews secret.

In my decades of performing and reviewing epidemiologic studies, I have never encountered a study in which the employer's attorneys conducted the worker interviews. This would allow unacceptable interference in the study and call into question the accuracy of the study's results. Even the presence of the employer's attorney in an interview would be problematic, since, in general, workers interviewed in studies are assured of confidentiality in order to elicit complete and truthful answers to the questions being asked.



Jonathan Sullivan
Alan Nadel
February 17, 2009

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privileged does not itself become privileged by communicating it to counsel.

If the interviews are conducted by Syngenta in-house legal counsel, it is likely that written summaries prepared of the interviews would be protected by either the attorney-client or the work-product privileges, as would the interviews themselves. The highest level of protection would be provided if the interviews were conducted by outside counsel. The United Kingdom, like the United States, recognizes that in-house counsel can have privileged communications with employees (or former employees) of the company by whom they are employed. The issue of to whom these communications can be communicated within the company while retaining their privileged character is still a matter of controversy in the United Kingdom, but like the United States, the communication must be for the purpose of rendering legal advice. Since the position of some EU (and non-EU) countries is more restrictive regarding the privileged nature of in- house counsel interviews, the safest course would be for outside counsel to conduct the interviews.

It is understood that Dr. Campbell's participation in the Widnes interviews is important to their success. Under American principles of privilege, Dr. Campbell's presence at the interviews, with inside or outside counsel, should not abrogate either the attorney-client or work-product privileges. The same result would most likely occur under United Kingdom principles, though the most secure method of ensuring that communications are privileged is if they occur only between counsel and the witness.

Various EU countries follow privilege principles that are substantially similar to the Anglo-American approach. For example, Denmark, follows the substantially same rule. Although France now appears to treat in-house and outside counsel alike, there still seems to be a lack of certainty regarding how French courts would treat this privilege issue.

Other EU countries such as Germany, and significantly Switzerland, follow slightly different rules as they relate to in-house counsel and it cannot be said with certainty that these types of communications (a) would enjoy the same level of privilege protection if conducted by in-house counsel in these countries, or (b) would be granted privileged status by the courts of these countries if litigation were instituted in these countries. For example, Switzerland makes the privilege available only to outside counsel. And while Germany permits in-house counsel to refuse to give evidence against their employers (when the evidence relates to

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(continued)

Jonathan Sullivan
Alan Nadel
February 17, 2009

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confidential matters that they conducted while employees) they must be admitted to practice law in Germany. This is not intended as a comprehensive review of the privilege rules of the entire continent, but one principle clearly emerges from an analysis of these countries: the highest level of protection is available for confidential communications between outside counsel and their client.

Additionally, while it might be expected that a conversation privileged in the country in which it occurs would also be treated as privileged in a court proceeding in a different country, this is not always the case. For example, if a forum court's law of privilege does not recognize the right of in-house counsel to conduct privileged communications, a court could likewise refuse to recognize the privileged nature of the communications as well. Therefore, the safest course. if litigation might be initiated outside the borders of the country in which the communications are to take place, is to follow the most conservative approach to these communications, which involves the use of outside, rather than inside counsel.

2. Lewis Smith has begun to discuss with me the prospect of Syngenta organizing to take a more proactive stance particularly with regulators on the claimed links between paraquat and parkinsonian symptoms. Specifically Lewis is looking at the possibility of a verbal presentation to the Toxicology Forum (see www.toxforum.org) of the peer review by a panel of external scientific experts (acting the request of Syngenta) of the published scientific and epidemiological studies, contained in a paper an advanced draft of which is attached. There is a lead time of several months to secure space on the agenda for meetings of the Toxicology Forum. You will see from the website that the next meetings of the Forum are in Aspen in July 2009, in Brussels in October 2009, and in Washington in February 2010. According to Lewis the audiences would include senior managers from EPA . The paper would be presented by one of the authors who would say that the authors had acted at the request of Syngenta.

Comment: The importance of proactively publicizing research studies that discredit the alleged connection between paraquat and Parkinson's disease is clear; however. the publication of an agenda for upcoming Toxicology Forum meetings that references Syngenta-sponsored research in this field conceivably could have adverse consequences.

For example, the public announcement in the Toxicology Forum agenda of an upcoming discussion of the Berry, La Vecchia and Nicotera research may increase the likelihood that their continuing (Syngenta-sponsored) work will come to the attention of (a) lawyers for claimants, and (b) anti-pesticide advocates such as NGOs. To the extent there is some public acknowledgment that the work of Berry, La Vecchia and Nicotera is

Mr. Wolff then addresses a separate question: Lewis Smith's proposal that Syngenta take "a more proactive stance … on the claimed links between paraquat and parkinsonian symptoms." Specifically, Dr. Lewis was advocating "proactively publicizing research studies that discredit the alleged connection between paraquat and Parkinson's disease." Wolff agreed that "the importance" of discrediting studies that had linked paraquat and Parkinson's disease was "clear."

So in this February 2009 memo, we have a lawyer choreographing scientific interviews and agreeing with a Syngenta proposal to discredit science linking paraquat and Parkinson's disease.

The memo continues with a discussion of Lewis Smith's upcoming move to part-time with Syngenta and part-time with the UK Medical Research Council (a publicly funded organization), where Smith would conduct laboratory research "on mice into the process of uptake of paraquat into the brain." The discussion focuses on some ways Syngenta could maintain confidentiality and privilege with respect to Lewis's work and communications and challenges that his divided employment might present.

8. 2009 Boston EET (External Epidemiology Team) meeting

In the following email exchange, we again see Dr. Smith attempting "to preserve the legal privilege" by routing email through in-house attorney Sullivan. He was reporting on the meeting in Boston with an expert epidemiology group (discussed earlier) – something Smith had proposed in his 2008 Paraquat Health Science Group Strategy Discussion Document. Attorney Sullivan was concerned that Dr. Dave Berry might have blown "any privilege which would otherwise attach to the report in U.S. litigation ... by Dave's having copied the report to others (who are not attorneys) when he sent it to" Sullivan. This appears to be just a ruse to create a phony claim of privilege for a report about a meeting between Syngenta employees and the non-Syngenta EET, consisting of the product defense experts Syngenta had or would commission to write papers for the scientific literature. And it again reveals that the scientists understood their instructions to try to preserve legal privilege even when it was clearly not applicable. In this instance, attorney Sullivan didn't even know the identities of the senior Syngenta stakeholders to whom he was supposed to forward the report. He had to ask Dr. Smith who they were.

502(d)-002426.0001

From: Smith Lewis CHBS
Sent: Dienstag, 10. März 2009 13:33
To: Sullivan Jonathan Dale CHBS
Cc: Nadel Alan USGR
Subject: RE: REPORT OF BOSTON MEETING

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Jonathan

Firstly, the intention of sending the reports to you, copied toothers, was to preserve privilege for the communication, although there shouldbe no 'hostages to fortune' in these reports. I had hoped that you wouldbe able to preserve the legal privilege in the correspondence you forwarded toothers. Obviously it is your call if you feel there is an unacceptablerisk in the short or medium term in forwarding these reports. Theintention had been to inform at least:

Sandro Aruffo
Sarah Hull
Robert Neale
Angela Brady
John Doe

of progress, but of course, you could decide to circulate it toothers including Rolf Furter and others in the Paraquat LeadershipTeam.

If you decide that this process does not add value then we will notcontinue with it.

Lewis

From: SullivanJonathan Dale CHBS
Sent: 09 March 2009 11:14
To: Smith Lewis CHBS
Cc: Nadel Alan USGR
Subject: REPORT OF BOSTON MEETING

1

CONFIDENTIAL - PARAQUAT LITIGATION 502(d)-002426.0001
SYNG_PARAQUAT_PRIV 03672 DOCUMENT SUBJECT TO 502(D)

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Lewis,

You will be aware because he copied it to you amongst others that I have received the report of the meeting with the expert epidemiologist group on 2 March which Dave Berry produced at my request and in response to a message which I sent to him on 26 February.
I am copying this message to Alan Nadel forhis advice as to whether any privilege which would otherwise attach to thereport in U.S. litigation is affected by Dave's having copied the reportto others (who are not attorneys) when he sent it to me.
It is my understanding that I would use thereport for the purpose of briefing a number of senior stakeholders in Syngentawho have indicated to you an expectation that such briefing would be provided.Please could you identify these stakeholders.

Regards,

Jonathan.

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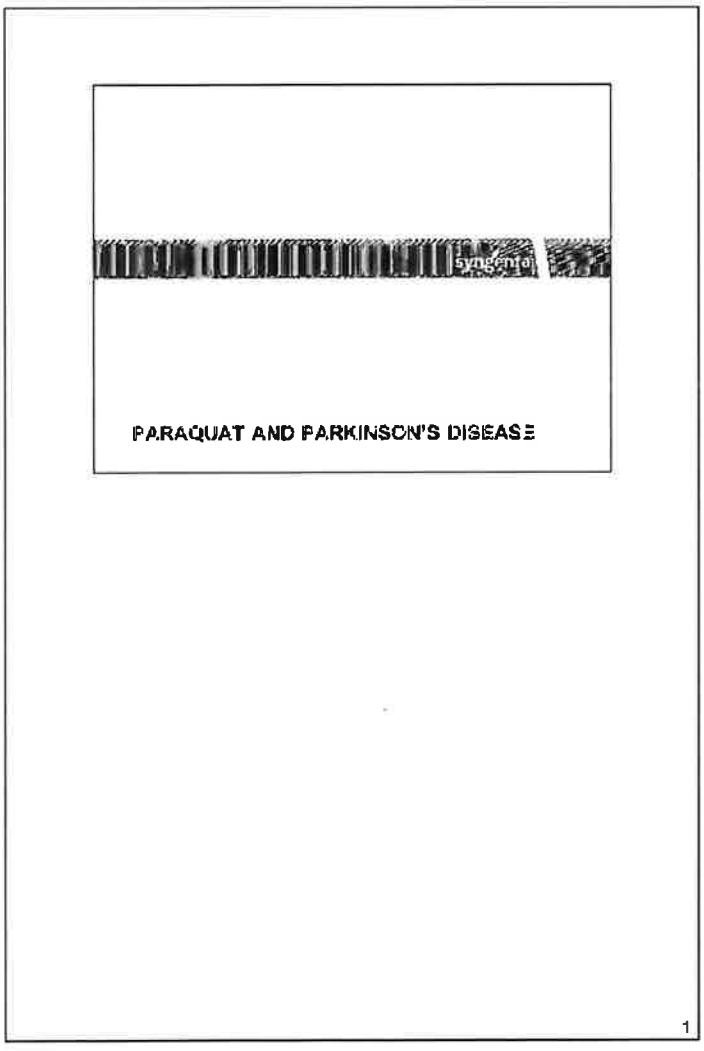
9. Wolff's edits of Dr. Smith's PQ/PD presentation

In 2009, Dr. Smith prepared a PowerPoint presentation entitled "Paraquat and Parkinson's Disease." Mr. Wolff reviewed it and expressed concern about "blunt statements" Dr. Smith makes in some slides. So, he recommends marking the presentation a "privileged communication," not due to its privileged nature, but "due to the blunt statements in some slides and the overall sensitive nature of the subject." Mr. Wolff even recognizes that "it is unlikely that the work product doctrine will attach to this presentation" but he still recommends that "given the sensitivity of the topic we believe it is worthwhile to include this footer"—in other words, mark the presentation as protected "work product" even though he does not believe it is. He also recommends limited circulation of the presentation ("it is not in Syngenta's interest for multiple copies of this document to be in circulation").

SYNG-PQ-02136022



SYNG-PQ-02136022

502(d)-002431.0001

From:	Sullivan Jonathan Dale CHBS
Sent:	06 May 2009 16:04
To:	Smith Lewis CHBS
Subject:	Comments on 5 6 09 Slides for PQ meeting / CONFIDENTIAL AND PRIVILEGED
Attachments:	Comments on 5 6 09 Slides for PQ meeting.DOC
Importance:	High

CONFIDENTIAL AND PRIVILEGED COMMUNICATION : DO NOT FORWARD, CIRCULATE OR COPY

Lewis,

I attach a memorandum containing the comments and suggestions which I have received from Jeff Wolff and Alan Nadel with respect to the slide set which you propose to use at tomorrow's meeting . I will incorporate the changes which they recommend into the slide set . I will then send one copy of the revised slide set to you and load one copy onto a USB stick for use at tomorrow's meeting . You will note the recommendation below that we do not circulate electronic copies of the slides or print paper copies for participants in the meeting . Likewise I would ask you not to copy or forward the slides to anyone else .

Jonathan .

-----Original Message-----
From: Wolff, Jeffrey [mailto:jwolff@fulbright.com]
Sent: Mittwoch, 6. Mai 2009 17:52
To: Sullivan Jonathan Dale CHBS
Cc: Nadel Alan USGR
Subject: Comments on 5-6-09 Slides for PQ meeting / CONFIDENTIAL AND PRIVILEGED

Jonathan:

Attached is a memorandum I prepared after a conference with Alan with comments and suggested revisions to the slides you and Lewis forwarded this morning.

Due to the blunt statements in some slides and the overall sensitive nature of the subject, we suggest including a footer which states: "Confidential / Privileged Communication"

We recognize it is unlikely that the work product doctrine will attach to this presentation; however, given the sensitivity of the topic we believe it is worthwhile to include this footer. With respect to distribution of the slides, for the reasons stated above, we advise that only a single electronic copy be presented via projection. It is not in Syngenta's interest for multiple copies of this document to be in circulation.

Let us know if we can be of further assistance.

Regards.

Jeff

Jeffrey S. Wolff
Fulbright & Jaworski

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The lawyers (Wolff and Nadel) made three pages of edits to the scientific content of the presentation. Nadel and Wolff's edits were incorporated into Lewis Smith's presentation. *See* 502(d)-

0107476.0001 (email with Lewis Smith's presentation attached, including attorney revisions.) So, once again, the judgment of the lawyers trumped the judgment of the scientist on scientific matters.

502(d)-002432.0001

Draft Comments on May 6, 2009 Slides on PQ and PD for Presentation to Leadership Team

(Prepared by Alan Nadel and Jeff Wolff. This document is confidential and protected by the attorney-client privilege)

Slide 3, bullet #3:

"Small percentage of genetic disease less than 5%, with the majority resulting from gene-environment or environmental causes."

[Suggest avoiding the emphasis in this statement on the role of environmental factors in causing PD. "Environmental causes" will almost always be interpreted by the public as man-made constituents such as PQ.]

Suggested rewrite:

"No single genetic mutation can account for most PD cases. The great majority of PD cases are idiopathic or of unknown cause."

[Alternate rewrite] "The majority of cases of PD are suspected to be caused by environmental factors interacting with genetic makeup."

Slide 4, bullet #2:

Suggested rewrite:

"PQ was mentioned in the Barbeau study because of its structural similarities to MPTP."

Slide 4, bullet #4:

Suggested rewrite

In the late 1990s and early 2000s Debbie Cory-Schlecter et al published several papers suggesting that PQ or PQ combined with ~~MANEB~~ Maneb could cause a loss of neurones ~~in from mice brains. The area affected was~~ the substantia nigra of mice brains.

Slide 5, title

Suggested rewrite:

"Background of Paraquat's alleged association with Parkinson's Disease"

Slide 6, bullet #2:

Suggested rewrite:

"Numerous papers have ~~now~~ been published on this issue, ~~the vast majority consistent in the~~ many of which claim that PQ can cause neuronal cell loss in the substantia nigra of mice by itself, or in combination with other chemicals."

Slide 6, bullet #3:

Suggested rewrite:

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"Because of PQ's alleged association with neuronal cell loss in mice, ~~does this~~ it is often described as a neurotoxin."

Slide 7, bullet #1:

Suggested rewrite:

"There have been numerous human studies evaluating the effect of pesticides on PD. Several studies suggest ~~These have usually shown that~~ pesticides may be are a risk factor for PD, but there is no it is doubtful if there is a strong association, and no or evidence that ~~they~~ pesticides cause PD."

Slide 7, bullet #2

"There are recent studies that claim to show exposure of unborn infants to PQ (those living in agricultural settings) and that exposure to PQ and MANEB increases the incidence of PD."

[Is this statement a reference to the meconium study? It suggests that the meconium study concluded that exposure of the fetus to PQ and Maneb increases the incidence of PD. I do not believe the study stated this.]

Suggested rewrite:

"There are recent studies ~~that~~ claim to show exposure of unborn infants to PQ ~~(those living in agricultural settings)~~ and that A recent study suggests that exposure to PQ and MANEB increases the incidence of PD. However, the pesticide exposure measurement used in this study is highly suspect."

Slide 8, title

"Our Challenge"

[This title suggests that we face a heavy burden to defeat the alleged PQ – PD connection. Suggested rewrite: "Our Scientific Objectives"

Slide 8, statement below title:

"The combination of experimental data and epidemiological data provides plausibility to the claim that PQ is implicated in PD."

[Suggest deleting this statement which could be viewed as an admission by Syngenta concerning the biologic plausibility of the claim that PD is caused by PQ. Suggest just stating the objectives.]

Slide 8, all bullets

[Suggest removing the "we have to" predicate text for all bullets, which carries a note of concern or anxiety.]

Examples:

~~We have to d~~Demonstrate that a scientifically based risk assessment provides reassurance that there is an acceptable margin of safety for those working with PQ.

~~We have to u~~Understand the mechanisms of action that contribute to the risk assessment and determine whether the effects in mice are qualitatively or quantitatively relevant to man.

[same for bullets on slide 9]

Slide 10, bullet #3:

"Our experts have written a review of the literature which will be published this year giving a more balanced appraisal of the relevance of pesticides (and PQ) to PD."

Slide 11, bullet #1:

"We have ~~agreed~~ to will publish an appraisal of the health status of a cohort of workers at Widnes. This will use death certificates to establish the prevalence of PD in those working on the 4,4'bipyridyl plant involved in PQ manufacture."

Slide 11, bullet #3:

"We have assessed the possibility of carrying out a case control study on PQ spray operatives in the USA to evaluate the relative incidence of PD. This study is unlikely to proceed as it does not offer sufficient power to add to the assessments already published or ongoing."

[Would this also be duplicative of the AgHealth study?]

Slide 12, bullet #1:

The majority of experimental studies are directed to ~~MoA~~mode of action.

[in case there are non-scientists in the audience.]

Slide 12, bullet #2

"Studies to repeat previous observations that show MPTP and PQ cause neuronal cell loss in the substantia nigra of mice."

[Do these studies confirm that the degree and amount of neuronal cell loss in mice is the same for MPTP and PQ? Should this statement be qualified?]

Slide 13, bullet #2:

"Determine the role of LPS in causing neuronal cell loss in the substantia nigra of mice."

[may be helpful to note what LPS is]

Slide 14, bullet #2 on left

Provide scientifically balanced critiques of published data that addresses the risk to those working with, or are, inadvertently exposed to, PQ

Slide 15, title:

"Positive Risk Factors Associated with PD"

[Given that Bipyridyls are listed here, consider whether the title of this slide should read: "Potential [or Suspected] Positive Risk Factors Associated with PD"

[Why is Maneb (alone) mentioned as a positive risk factor for PD?]

10. Wolff changes Science in Smith's PQ/PD Presentation

In June 2009, attorney Wolff makes changes to substantive science in Lewis Smith's PowerPoint slides. He also suggested marking the slides confidential and privileged to shield this business document from being turned over in litigation.

502(d)-000431.0001

From: Sullivan Jonathan Dale CHBS
Sent: 19 June 2009 15:36
To: Smith Lewis CHBS
Subject: PQ/PD SLIDES

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Lewis,

Attached are the comments from Jeff Wolff on your draft slides dealing with decision tree / timelines .
Please could you incorporate these changes into the slides and send the revised version to me (only) .
For the meeting with Gerardo next week I suggest we show him the slides on my laptop and do not print copies .
Are you also proposing to use the slide set from which you presented at the May 7 meeting - if so I recommend we handle this slide set in the same way ?

Regards,

Jonathan

From: Wolff, Jeffrey
To: Sullivan Jonathan Dale CHBS; Nadel Alan USGR
Sent: Fri Jun 19 15:29:54 2009
Subject: RE: PQ/PD SLIDES
Jonathan:

Alan and I have discussed Lewis's draft slides depicting the decision tree / timeline for the company-sponsored PQ studies and offer the following comments:

First it is highly unlikely the slides or the meeting discussing the slides would be considered protected by the attorney-client privilege. Even if the slides were created at the request of counsel, they do not appear to constitute the delivery of legal advice. To the contrary, the topics addressed in the slides are clearly scientific and technical (i.e., discussions of Glial cell activation and summaries of biological response studies). Further, the slides are directed at a scientific audience: Syngenta's Health Science Team.

With respect to whether the work product privilege applies, we have a colorable argument in support of this privilege. But if Syngenta's privilege claim is later challenged, Syngenta would have the burden to demonstrate that the slides (and the studies) were generated for the purpose of defense of litigation rather than for a business purpose.

In order to improve the chances of protecting the slides and the accompanying discussion from discovery it is suggested that: (1) the footer be on the slides be modified to state: "Privileged and Confidential – Prepared at Request of Legal Counsel" (2) all meeting participants be instructed to clearly label their meeting notes as "privileged and confidential," and (3) hard copies of the slides should not be circulated.

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Dr. Smith sends the PowerPoint slides to Jonathan Sullivan.

Attached is a first draft of the slides depicting the decision tree / timeline for the company-sponsored studies, which I had asked Lewis to produce .

I should be grateful if you would review these and let me have your comments .

Lewis is suggesting that he would like to use these slides at a meeting with Gerardo Ramos, who has recently taken over Rolf Furter's former role as Head of CP Development, which I have scheduled to take place here on 26 June, in order to bring Gerardo up to speed . I will also attend this meeting and Lewis is making the assumption that the slides will automatically be privileged by virtue of my presence – this seems unlikely to me and what is perhaps more important is that the slides have been created at my request . I should be grateful for your guidance as to how the slides should be handled to optimize our prospects of maintaining a claim of privilege (for example should Gerardo be allowed to retain a paper copy of the slides or should he return them to me at the end of the meeting ?)

Regards,

Jonathan .

From: Smith Lewis CHBS
Sent: Donnerstag, 18. Juni 2009 14:04
To: Sullivan Jonathan Dale CHBS
Subject: FW: PQ/PD SLIDES

Jonathan

This is the first draft of the slides you requested. Only 1 to 9 will be used and if you agree to content we shall have them more professionally prepared to make the presentation slick.

For Gerardo's meeting I would like to use these along with some background slides we have used in the past. As you will be there the meeting will be Privileged and Confidential so I trust that will be ok.

Lewis

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In-house counsel Sullivan then sends the slides on to Jeff Wolff asking him how to make sure they retain privilege over them. And then Wolff recommends changes to slides 5, 6 and 10.

The following are specific comments on the sides:

Slide 5: I'm not sure I understand this slide but I'm concerned by the graphic which suggests that PQ exposure leads to cell death and direct damage to neuronal cells in the absence of the intervention of an anti-inflammatory drug. Can this be modified?

Slide 6: I recommend removing the statement: "(We can show loss of cells in SNpc and neurotransmitter effect)' simply because it is an unhelpful admission verifying unhelpful claims which have been made in the literature about PQ. This observation can be made verbally during the presentation.

Slide 10: This slide contains a statement: "Agents – Short List." Does this mean that PQ is on a short list of agents suspected to cause PD? If so, I would suggest removing this potentially damaging admission from the slide and making the observation verbally.

Let us know if we can be of further assistance.

Regards.

Jeff

Jeffrey S. Wolff
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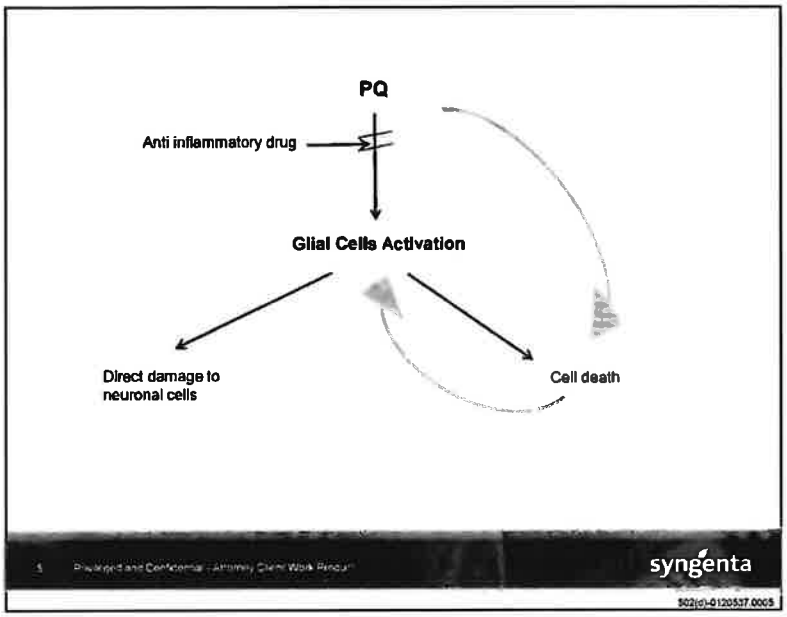
1301 McKinney
Suite 5100
Houston, TX 77010-3095
Phone: 713-651-5466
Fax: 713-651-5246
jwolff@fulbright.com

ORIGINAL SLIDE 5 (502(d)-0120537.0001 at 5)



Wolff's comment re original slide 5:

Slide 5: I'm not sure I understand this slide but I'm concerned by the graphic which suggests that PQ exposure leads to cell death and direct damage to neuronal cells in the absence of the intervention of an anti-inflammatory drug. Can this be modified?
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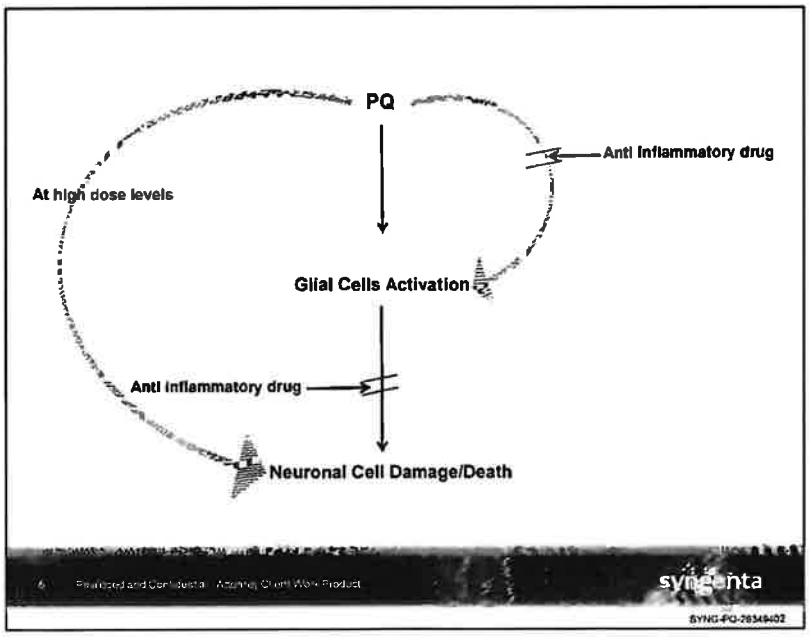
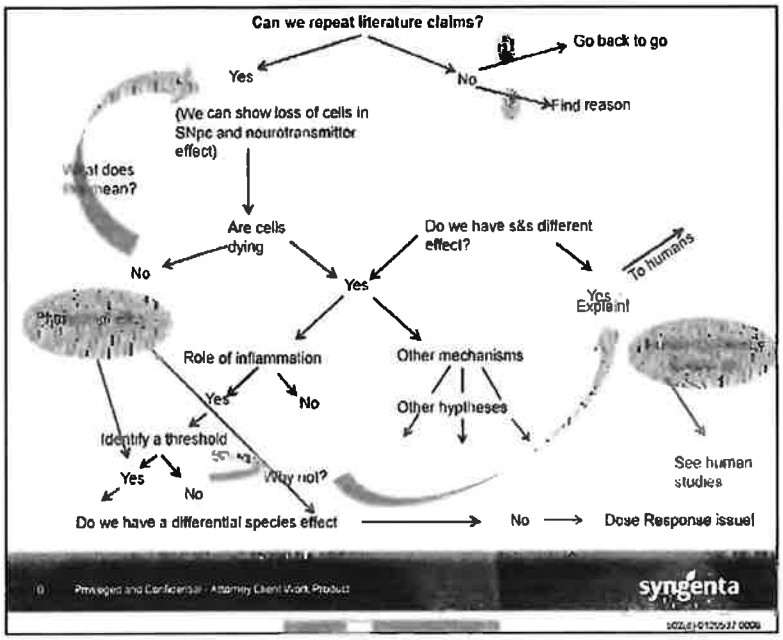
REVISED SLIDE FIVE (SYNG-PQ-29349398)



ORIGINAL SLIDE 6 (502(d)-0120537.0001 at 6)



Wolff's comment re original slide 6:

Slide 6: I recommend removing the statement: "(We can show loss of cells in SNpc and neurotransmitter effect)" simply because it is an unhelpful admission verifying unhelpful claims which have been made in the literature about PQ. This observation can be made verbally during the presentation.

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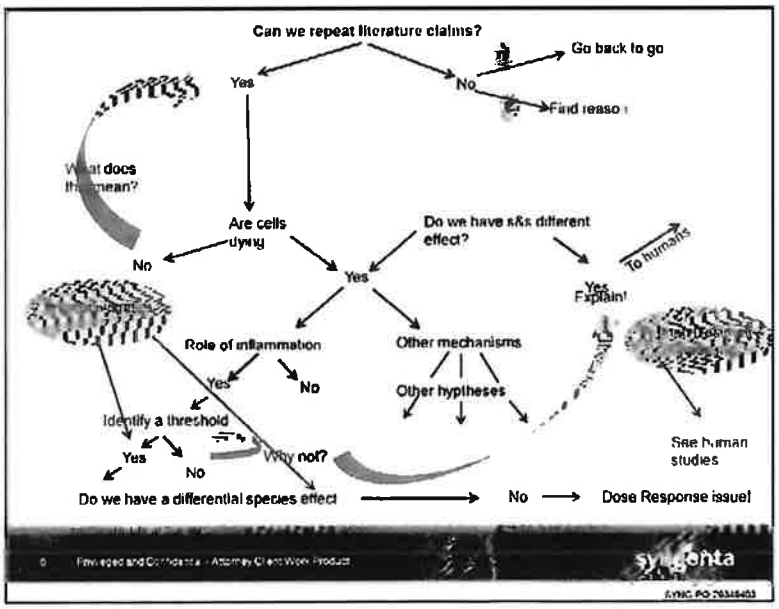
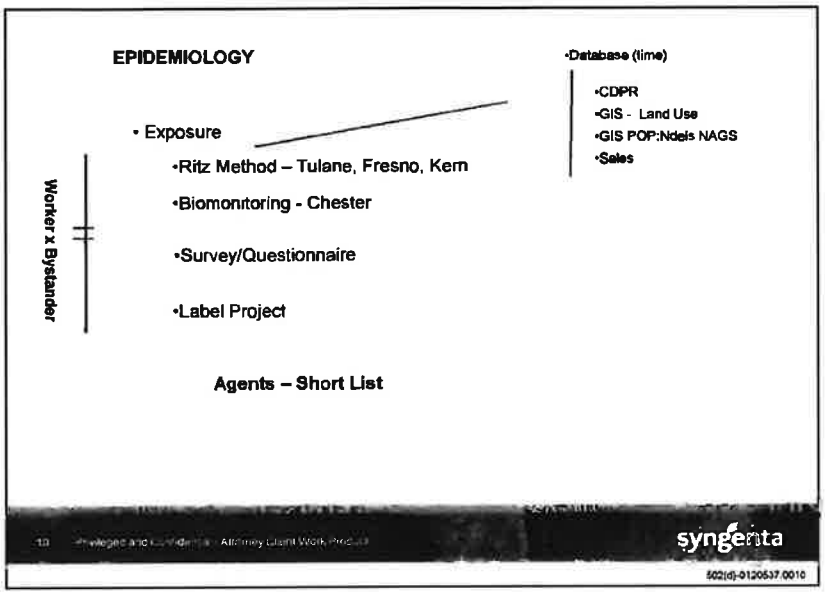
REVISED SLIDE 6 (SYNG-PQ-29349398)



ORIGINAL SLIDE 10 (502(d)-0120537.0001 at 10)



Wolff's comment re original slide:

Slide 10: This slide contains a statement: "Agents – Short List." Does this mean that PQ is on a short list of agents suspected to cause PD? If so, I would suggest removing this potentially damaging admission from the slide and making the observation verbally.
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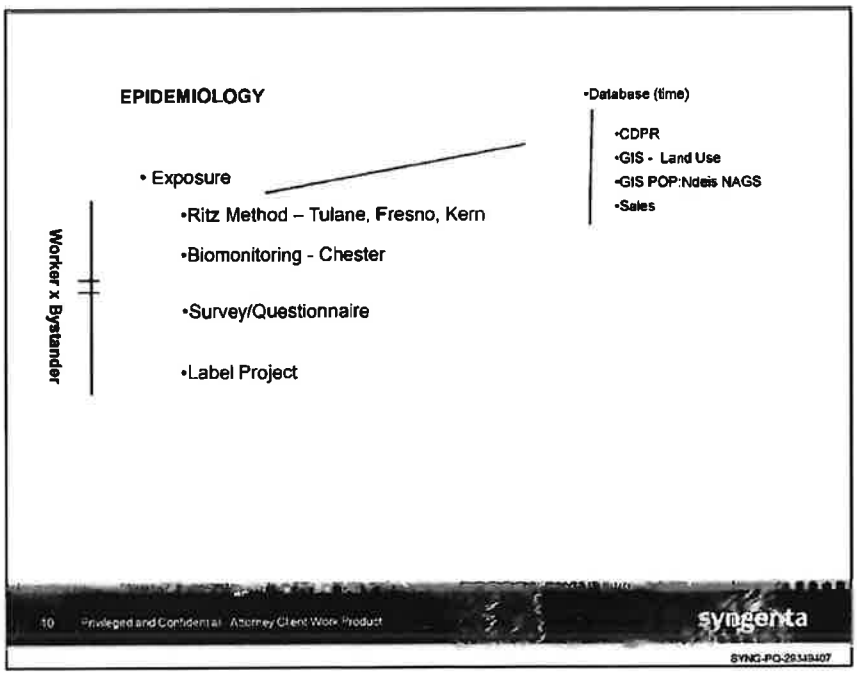
REVISED SLIDE 10 (SYNG-PQ-29349398)



So, Mr. Wolff's preferences prevailed over what the scientists wrote in these three slides. In Slide 5, the graphic showing cell death and direct damage is changed to mask death and damage. In Slide 6 an "unhelpful admission" is removed, not because it is inaccurate, as demonstrated that the point can be made verbally during the presentation. Likewise, in Slide 10 a "damaging admission" is removed, not because it was incorrect but because it was a "damaging admission."

H. Syngenta distorts the scientific picture

1. Breckenridge 2013 study

As part of the research workplan that Dr. Smith proposed in 2008, Dr. Charles Breckenridge conducted a new mouse study. His research, unlike that of Dr. Marks, was published in 2013. Syngenta's description of Dr. Breckenridge:

> 8. **Charles Breckenridge, Ph.D. (Former Senior Science and Technology Fellow, SCPLLC, Former PHST Member).** Dr. Breckenridge was one of SCPLLC's most experienced and knowledgeable authorities on paraquat health and safety issues, including human health, research in mammals, and toxicology. Dr. Breckenridge served as a member of the Paraquat Health Sciences Team ("PHST"). Senior managers at SCPLLC relied on the advice of Dr. Breckenridge and did not make a decision related to paraquat in the areas of toxicity and safety without consulting Dr. Breckenridge.

And in his study, Dr. Breckenridge found that paraquat was *not* neurotoxic in the mouse.[159]

Dr. Breckenridge and his coauthors did not acknowledge the existence of Dr. Marks's mouse studies, even though those coauthors included Dr. Nicholas Sturgess (a colleague of Dr. Marks who presented her work at the Atlanta 2008 meeting), and Dr. Lewis Smith (Sturgess's and Marks's superior who had consulted with both Sturgess and Marks regarding that research). By ignoring Dr. Marks's work, Dr. Breckenridge and his coauthors did not have to reconcile their study with hers because no one outside of Syngenta knew about Dr. Marks's studies.

2. Minnema 2014 study

Syngenta's Dr. Daniel Minnema (an employee of Syngenta Crop Protection in Greensboro, North Carolina) published a second mouse study in 2014. (Minnema was one of the coauthors of Breckenridge's 2013 study, and Breckenridge was one of Minnema's coauthors. In fact, all of the same coauthors appeared on both studies). In his study, Dr. Minnema found that feeding paraquat to mice for 13 weeks did not result in loss of brain cells. In other words, like Breckenridge's study, Minnema's study purported to find that paraquat is not neurotoxic in mice.[160] As with Breckenridge's study, Minnema's 2014 study did not acknowledge the existence of Dr. Marks's work.

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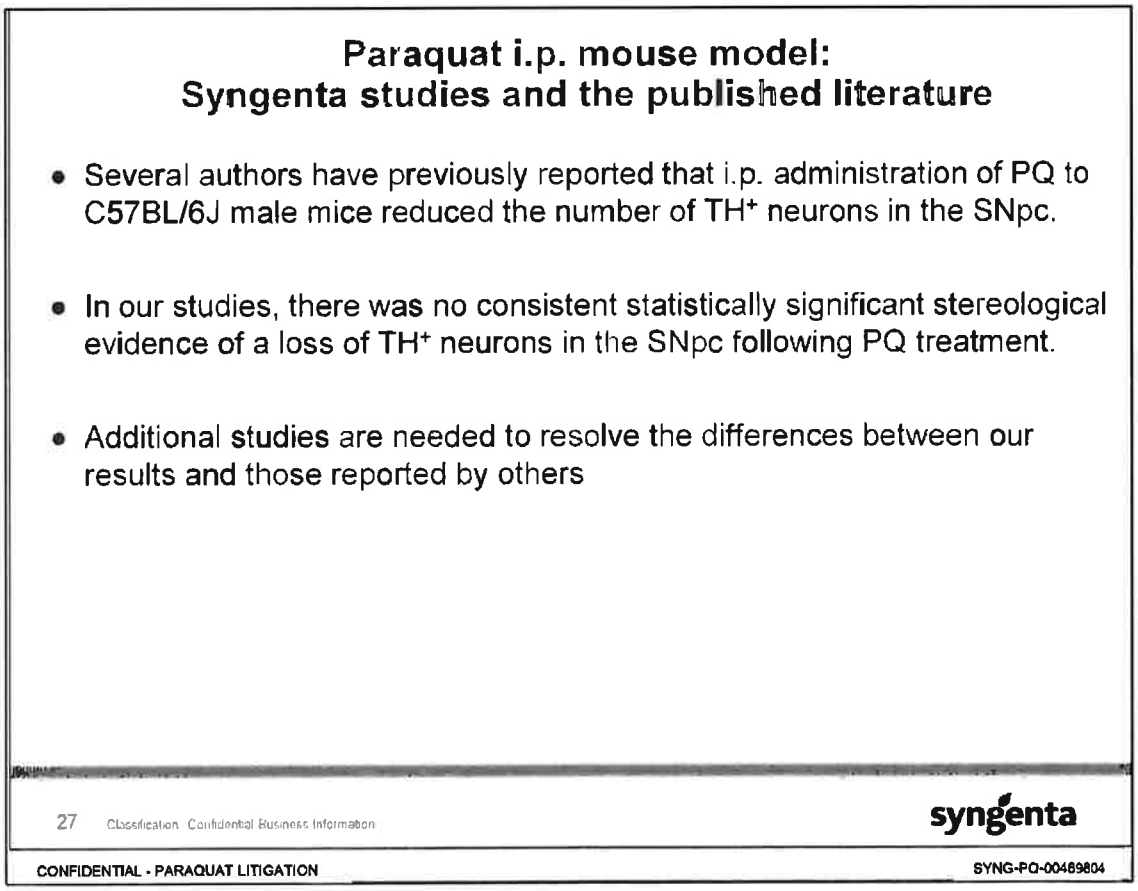
[159] SYNG-PQ-00480951 (Breckenridge, et al. (2013)).
[160] SYNG-PQ-01211363 (Minnema, et al. (2014)).

I. Syngenta lies to the EPA in 2013 and 2017

In February 2013, several Syngenta employees (Monty Dixon, Jerry Wells, Kersten Mewes, Charles Breckenridge, and Nick Sturgess) met with and made a presentation to the EPA. The presentation addressed the EPA's review of paraquat's eligibility for re-registration.[161]

In that presentation, Syngenta told the EPA, "In our studies, there was no consistent statistically significant stereological evidence of a loss of TH+ neurons in the SNpc following PQ treatment." *Slide 27*. In truth, in only *some* of Syngenta's studies "there was no consistent statistically significant stereological evidence of a loss" of TH-positive neurons in the substantia nigra pars compacta following paraquat treatment. While the statement was true of the 2013 and 2014 Breckenridge/Minnema studies, it was just the opposite of Dr. Marks's earlier findings. Syngenta did not disclose Dr. Marks's studies to the EPA at or before the February 2013 meeting.

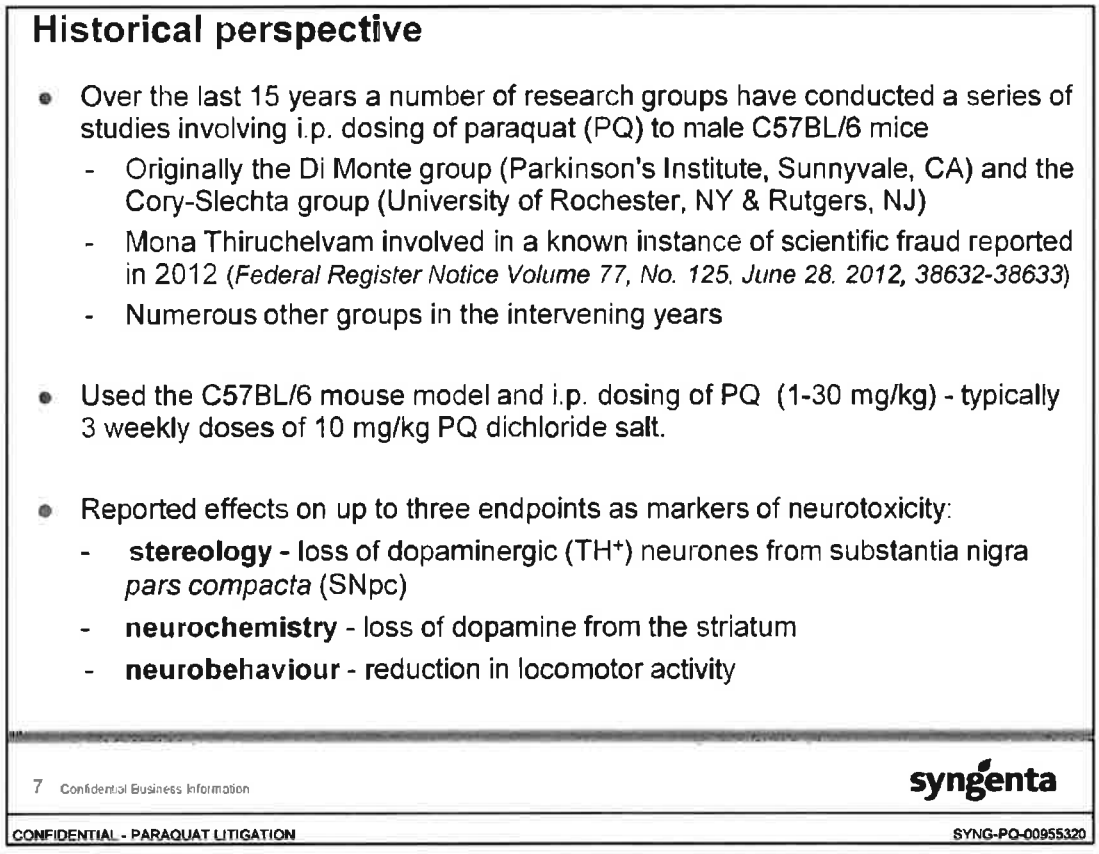
SYNG-PQ-00469778 (slide 27 from 2013 presentation to EPA)



[161] (paraquat is currently undergoing a review, docket number EPA-HQ-OPP-2011-0855).

Four years later, most of the same group meets with the EPA a second time. This time Syngenta makes a presentation to the EPA discussing studies that have been conducted "over the last 15 years."

SYNG-PQ-00955314 (slide 7 of 2017 EPA presentation)



Historical perspective

- Over the last 15 years a number of research groups have conducted a series of studies involving i.p. dosing of paraquat (PQ) to male C57BL/6 mice
  - Originally the Di Monte group (Parkinson's Institute, Sunnyvale, CA) and the Cory-Slechta group (University of Rochester, NY & Rutgers, NJ)
  - Mona Thiruchelvam involved in a known instance of scientific fraud reported in 2012 (*Federal Register Notice Volume 77, No. 125, June 28, 2012, 38632-38633*)
  - Numerous other groups in the intervening years
- Used the C57BL/6 mouse model and i.p. dosing of PQ (1-30 mg/kg) - typically 3 weekly doses of 10 mg/kg PQ dichloride salt.
- Reported effects on up to three endpoints as markers of neurotoxicity:
  - **stereology** - loss of dopaminergic (TH^+) neurones from substantia nigra *pars compacta* (SNpc)
  - **neurochemistry** - loss of dopamine from the striatum
  - **neurobehaviour** - reduction in locomotor activity

7 Confidential Business Information

syngenta

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQ-00955320

And Syngenta tells the EPA that "Syngenta conducted a series of studies in an attempt to replicate the results from published studies." Once again, however, Syngenta did not disclose to the

EPA Dr. Marks's work, which was conducted during that 15-year time period. At slide 53, Syngenta told the EPA "There are No Effects of Paraquat in Animal Models"? The presentation notes show that Syngenta told the EPA:

> There are No Effects of Paraquat in Animal Models
>
> We have consistently found that paraquat
>
> Does not reduce dopamine levels or increase dopamine turnover in the striatum.
>
> Does not reduce the number of TH+ neurons in the SNpc.
>
> Does not cause neuronal cell death in the SNpc, (i.e. absent of effect on AmCuAg, TUNEL or Caspase 3)
>
> Does not activate microglia (IBA-1) or astrocytes (GFAP).
>
> We found that MPTP consistently affects neurochemistry, stereology, and neuropathology in the SNPc and striatum.
>
> SYNG-PQ-00955366

But just as in 2013, Syngenta's 2017 EPA presentation was untrue because it omitted the Marks studies that had found just the opposite.

J. Syngenta's behind-the-scenes influencing of Debbie Cory-Slechta nomination to EPA'S FIFRA Science Advisory Panel (SAP)

The EPA's FIFRA Scientific Advisory Panel ("SAP") provides independent scientific advice to the EPA on health and safety issues related to pesticides. (https://www.epa.gov/sap) The SAP is comprised of biologists, toxicologists, and other experts who provide valuable information and opinions on critical aspects of pesticide safety. The SAP is extremely important and influential regarding the regulation of pesticides used in the United States. It is obviously very important that this critical panel not be subject to influence from the very companies whose products the panel has responsibility to review, as even Syngenta recognizes. *See* 6/17/20 Botham Tr. Vol. III at 665-66; *see generally ibid. at* 663-707.

In the late 1990s and early 2000s, Dr. Debra Cory-Slechta, a professor of environmental medicine at the University of Rochester Medical School, began researching and publishing scientific articles suggesting a link between paraquat exposure and the development of Parkinson's disease. Internal documents reveal that Syngenta scientists repeatedly targeted Dr. Cory-Slechta because they perceived her work as a threat to the continued viability of paraquat products. By 2003, Syngenta scientists and other employees had settled upon an influencing strategy plan, a part of which included influencing regulators.

In late 2004, Syngenta employees learned that Dr. Cory-Slechta might be appointed to the SAP.[162] In June 2005, the National Science Foundation officially nominated Dr. Cory-Slechta to fill a vacancy on the SAP.[163] Syngenta employees, including some of the highest level scientists

[162] Botham Ex. 57 (SYNG-PQ-04206065-67).
[163] Botham Ex. 58 (SYNG-PQ-05705351-52).

in the company, worked to block her nomination.[164] Ultimately, these Syngenta employees drafted written objections to Dr. Cory-Slechta's nomination that they secretly funneled through Ray McAllister of CropLife America.[165] McAllister, in turn, sent these criticisms of Dr. Cory-Slechta to his contacts at the US EPA.[166] The efforts were successful and Dr. Cory-Slechta was not appointed. The communications between McAllister and Syngenta disclose their efforts to conceal Syngenta's role in this process.[167]

In 2010, the National Science Foundation again nominated Dr. Cory-Slechta to become a member of the SAP.[168] As they had done in 2005, Syngenta sprang into action to defeat Dr. Cory Slechta's appointment.[169] Once more Syngenta reached out to Ray McAllister of CropLife America. On September 3, 2010, CropLife America submitted its comments to Dr. Frank Sanders, Director of the US EPA's Office of Science Coordination and Policy.[170] Without informing the EPA of Syngenta's role in the letter, CropLife America adopted word for word the objections written by Syngenta employees. No Syngenta employee's identity was ever revealed.

K. "Exponent is generally industry friendly"

SYNG-PQ-11605631

From: Nadel Alan USGR
Sent: Thursday, February 25, 2010 2:56 PM
To: Sullivan Jonathan Dale CHBS
Subject: RE: ATRAZINE / PARAQUAT

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Jonathan:

1) I have accepted the meeting invitation for the call with Philippe.
2) I don't necessarily have a problem with Lewis and other Syngenta scientists having these kinds of discussions with non-Syngenta scientists as long as they involve information which we intend to make public in relatively short order. Exponent is generally industry friendly in any event. I would, however, be a lot less comfortable if we had replicated the Cory-Schlecta findings and Lewis divulged that before we had a plan in place to deal with it.
3) I will call Jeff regarding the week of May 17. I have a problem at the beginning of that week, but could be available Wed. or later.
4) I will mention Richard's comment to Jeff when I speak with him today.

Regards,

Alan

SYNG-PQ-11605631

[164] Botham Ex. 59 (SYNG-PQ-05705349-50).
[165] Botham Ex. 60 (SYNG-PQ-05707254).
[166] Botham Ex. 61 (SYNG-PQ-00353198-204).
[167] Botham Ex. 62 (SYNG-PQ-00355434).
[168] Botham Ex. 63 (SYNG-PQ-22717989).
[169] Botham Ex. 64 (SYNG-PQ-ATR-07709192).
[170] Botham Ex. 65 (SYNG-PQ-ATR-06489282-83).

(2) Also on February 4 on my regular weekly call with Lewis Smith, Lewis said (following his message of 22 January regarding relationships with different groups of external scientists, which I forwarded to you and Matthew Bayliss) that Syngenta personnel (including presumably Lewis himself) had discussed with representatives of Exponent, amongst other groups of external scientists not contracted to work for Syngenta and not otherwise bound by any obligation of confidentiality to Syngenta, the fact that Syngenta had carried out its own study using IP administration of paraquat to the C57Bl6J mouse strain and had been

SYNG-PQ-11605631

unable to repeat the findings of the Cory-Schlecta group study . Lewis characterized this dialogue as a normal part of a working scientific process in which Syngenta would routinely "compare notes" with reputable scientists known to be undertaking research in the same area (and by inference not known to be actively hostile to Syngenta or paraquat) . Lewis sought to draw a distinction between business –critical information and what he described as "scientific information which has to be the subject of open dialogue" . I should be grateful for your views on this and if appropriate I will schedule a call also among the two of us and Lewis

(3) When I spoke to Lewis yesterday, also on one of my regular weekly calls with him, he said that based on the latest enquiries made by Judith Burton the most feasible timing for the postponed Health Science Team meeting appeared to be during the week commencing 17 May when Lewis himself will be in the U.S. for another meeting, but that he understood that Jeff Wolff had signaled a conflict in that week . It would be helpful if you could have a word with Jeff to help us to understand his conflict and whether there is any possibility of removing it . We could of course go ahead without Jeff, but I anticipate that this meeting will be particularly critical in terms of decision-making and the path forward . I don't know whether Jeff's conflict is in any way tied to the location of the meeting but at the moment as I understand it the most likely venue is GSO . After I finished talking to Lewis I saw from my notes that earlier in the conversation he had told me that EPL had now committed to complete the reading of the slides from the repeat study using the "QUID" process by April 18 and using stereology by May 17, so the timing of the Health Science Team meeting which Lewis is proposing in any event looks quite tight, but I have not been back to Lewis on this

SYNG-PQ-11605632

EXPONENT CHERRY PICKS STUDIES FOR SYNGENTA

SYNG-PQ-00126462

From: Breckenridge Charles USGR [mailto:charles.breckenridge@syngenta.com]
Sent: Monday, February 16, 2015 3:51 PM
To: Ellen Chang
Subject: Study Exclusion

SYNG-PQ-00126462

Ellen: For paraquat, would you please provide me with the list of studies that are co-dependent for each specific investigative groups.

The bottom line is if we applied our rules, which studies would be asterisked and not use in a meta-analysis calculation and which one of a series would be used.

I could go back to a slide pack that Jack presented on this topic but, I want to get it right the first time since it takes Bob considerable time to recalculate all the parameters for a data set. The trim and file procedure is especially onerous because it is an iterative process.

If the rules for study inclusions have been bent for the other scenarios, then you should provide those as well.

Thanks

CBB

From: Ellen Chang <echang@exponent.com>
Sent: Monday, February 16, 2015 4:43 PM
To: Breckenridge Charles USGR
Subject: RE: Study Exclusion

Dear Charles,

Here are the overlapping studies for paraquat, which was the only exposure for which the rules for overlap were bent.

California Central Valley study:
Costello 2009
Gatto 2009
Lee 2012
Ritz 2009
Wang 2011

Among these five, if I were to choose one RR, I would choose that from Lee 2012, which included more controls and reported on ambient residential and occupational exposure to paraquat combined.

Group Health Cooperative study:
Firestone 2005
Firestone 2010

Between these two, I would choose the RR from Firestone 2010, which includes more cases and controls than Firestone 2005.

FAME nested case-control study in AHS:
Tanner 2011
Goldman 2012

Between these two, I would choose the RR from Tanner 2011, because that from Goldman 2012 is restricted to subjects with genotyping data (i.e., Tanner 2011 includes more cases and controls).

Obviously, the co-authors need to agree on how to deal with these. I defer to those of you who have far more experience on the subject of paraquat and PD. The problem with the choices that I've identified above is that, in all instances, the RR is lower (closer to the null) than other RRs, and could therefore be perceived as biased.

Best wishes,
Ellen

SYNG-PQ-00126462

IV. Summary of Opinions

In my opinion, Defendants engaged in a series of continuous and interrelated unethical, unscrupulous and at times downright fraudulent acts and practices extending over several decades to maintain their ability to sell paraquat. Defendants' scheme has evolved over the years, but the principal goal has remained unchanged -- to keep paraquat on the market so they could continue to reap corporate profits at the expense of human lives.

In summary, Defendants have followed the corporate product defense strategy outlined earlier in this report almost to the letter. They were fully aware of many of the hazards of using paraquat before it was first sold in the U.S. They became increasingly aware of even more dangerous hazards throughout the 1960s. They were fully aware that paraquat's mode of action gave it the potential to be a neurotoxin and that it would end up in the brains of users when used as intended. They were fully aware that there was no real way to completely protect users from exposure to paraquat when used as intended. But instead of thoroughly testing the product to ensure it could be used safely without threat to the human brain, they buried their heads in the sand and ignored the unequivocal signs of neurotoxic danger that were being telegraphed both by independent and their own scientists. Further, Defendants' functional monopoly over the paraquat market put them in a unique position of having virtually exclusive access to all the material facts about the dangers of paraquat. In essence, Defendants were the only ones in the world with the ability to connect all of the dots, but they willfully refused to make that connection and continue to deny it to this day.

The evidence in this case makes clear to me that Defendants' failure to share their knowledge of scientific evidence of paraquat's toxic effects on the central nervous system with regulators and the public was deliberate, deceptive and done with the intent to protect paraquat sales. Syngenta has baldly admitted knowing that if a causative connection between paraquat and Parkinson's disease was established, it would threaten future paraquat sales. Syngenta therefore launched a comprehensive "influencing strategy" to hide the truth and protect those sales. Corporate influencing strategies can be ethical. Syngenta's was not. Knowing that the public would view the presence of paraquat in the brain negatively, Syngenta scientists were instructed to avoid testing for paraquat in the brains of test animals. Syngenta paid scientists to create studies to distort the scientific picture in the hopes of generating reasonable doubt about the connection between paraquat and Parkinson's disease. Syngenta engaged in a deceptive campaign with a corporate trade association to derail the appointment of a scientist they viewed as unsympathetic to their toxic chemical to the EPA's Scientific Advisory Panel on paraquat. Syngenta deliberately and unethically employed the attorney-client privilege to keep damning information about their toxic product a secret.

Syngenta viewed independent scientific studies that were making a key link between paraquat and Parkinson's disease as a "threat." So, Syngenta conducted its own studies to try to refute them. When Syngenta's own studies instead confirmed the findings of the independent scientists, Syngenta deliberately hid them from the public and the EPA and then lied about their existence in later conversations with regulators. Syngenta also failed to disclose to the EPA or the public damning results from studies conducted in non-human primates, knowing the findings are more applicable to humans. Our public policy, as embodied in FIFRA and its regulations regarding duties and responsibilities of pesticide manufacturers, mandates honest reporting if the "registrant

has additional factual information regarding unreasonable adverse effects on the environment of the pesticide...." Syngenta's flagrant violations of FIFRA reporting obligations clearly offend public policy.

The most disheartening evidence in this case, to me, is Defendants' callous deception regarding the effectiveness of their emetic. Assuming the facts are true as I was asked to do, these Defendants, faced with the real risk of a paraquat ban by regulators, filed manipulated data with regulators to convince them that the emetic was effective and would save lives. Defendants knew that was not true and knew the data supporting their emetic concentration estimates was at best "weak" and at worst, had been falsified. Hundreds of people have died unnecessarily because Defendants did not want to incur the expense of adding enough emetic to make it effective. Their conduct regarding the emetic is the very definition of unethical and unscrupulous.

The mere act of putting paraquat on the market for sale is telling purchasers, like the Plaintiffs, that paraquat is reasonably safe for its ordinary and intended use. Implicit in that statement is a representation that Defendants have adequately tested and assessed the risks and potential hazards of paraquat use and have been honest and transparent in sharing their knowledge with regulators. The importance of such a representation is emphasized by the testimony of each of the three Plaintiffs who testified that they would not have bought paraquat have they known it causes Parkinson's disease. In all of the fifty-five years it has been sold in this country, neither Defendant has ever warned users of paraquat's neurotoxic potential or that paraquat will get into your brain when used as intended.

Clearly, Defendants' conduct has resulted in substantial, indeed grave, injury to the Plaintiffs, consumers, and the public at large. All of the Plaintiffs here are suffering from Parkinson's disease. As Defendants have admitted in their depositions, Parkinson's disease is a slowly progressive, debilitating, and incurable neurological disorder. More than 10 million people worldwide are living with Parkinson's disease. As many as one million Americans live with Parkinson's disease, which is more than the combined number of people diagnosed with multiple sclerosis, muscular dystrophy and Lou Gehrig's disease. The costs associated with Parkinson's treatment are an extreme burden on its victims and society. Medication costs for an individual person with PD average $2,500 a year, and therapeutic surgery can cost up to $100,000 dollars per patient. The combined direct and indirect cost of Parkinson's, including treatment, social security payments and lost income from inability to work, is estimated to be nearly $52 billion per year in the United States alone. Much of the cost of the disease is borne by the Medicare and Medicaid programs, because the population suffering from Parkinson's disease is largely comprised of older persons of lower income. There is absolutely no benefit to the advancement of science or public health in distorting the science to preserve corporate profits and shift the tremendous costs to unsuspecting users, the health insurance system and public programs like Medicare, Medicaid and Social Security Disability. Finally, paraquat users could not have avoided the injury for the simple fact that they were unaware of the neurotoxic risk posed by long-term exposure to paraquat due to Syngenta and Chevron's deliberate disinformation campaign. If consumers knew the true nature of their risks in using this weed killer, i.e., had they known what Syngenta and Chevron have known for fifty years, they could have made an informed choice about whether to use paraquat at all.

Date July 10, 2020

By: _____

DAVID MICHAELS, Ph.D., M.P.H.

APPENDIX A

SYNG-PQ-00474675:

- The RDT recommends not progressing with a definitive developmental neurotoxicity study at this time as the methodology is still subject to change and there is no clear timeline of regulatory need
- The RDT encourages proactive careful consideration of the appropriate design and timing for conduct of a future paraquat developmental neurotoxicity study

2. Monitor, understand and influence ongoing academic PD research and manage the impact on paraquat registrations by putting published findings in context of the use of paraquat as a herbicide
   - Develop and maintain an in-house capability to further our understanding of paraquat and its role in PD models, and to gain a presence in the international scientific community engaged in this PD research
   - Foster close links with the key relevant PD research groups globally to get early visibility of their research and potential publications, and create opportunity to influence these to avoid inadvertently alarmist statements or misleading conclusions based on a poor understanding of paraquat's use as a herbicide
   - Review relevant publications and advise the RDT of key findings and potential risks from anticipated future research

3. Support regulatory authorities in dismissing the hypothesis that paraquat is a risk factor for Parkinson's Disease in humans
   - Maintain PD position statements and literature reviews and make these available to regulatory authorities as appropriate
   - Seek to demonstrate the lack of independent regulatory expert support for the hypothesis that paraquat residues in food is a risk factor for PD in the general population
   - Formally include PD in the WHO periodic re-evaluation of paraquat toxicology under JMPR in 2003

4. Seek to demonstrate the lack of independent regulatory expert support for the hypothesis that occupational paraquat exposure is a risk factor for PD in the sub-population of people exposed to paraquat
   - Monitor, and where appropriate contribute to, national regulatory consideration of the association between PD and rural living, pesticides in general and paraquat specifically

5. Create an international scientific consensus against the hypothesis that paraquat is a risk factor for Parkinson's Disease in humans
   - Demonstrate how low aggregate exposure of the general population to dietary residues of paraquat from food and drinking water really is by conducting and publishing a US market basket residue survey and a relevant water monitoring exercise
   - Demonstrate the difference (in orders of magnitude) between doses of paraquat causing observed, and relevant, biological effects and paraquat exposure to the sub-population in and around its occupational use as a herbicide
   - Emphasise alternative agents or risk factors that have both a hazard and exposure profile that make them a more plausible lead for targeted academic PD research

SYNG-PQ-00474676|

SYNG-PQ-02036738:

Paraquat registrations will remain insecure and will require considerable proactive defence. Global, regional and country Critical Success Factors are proposed and it is strongly recommended that these become objectives for the business and regulatory managers concerned during 2004 and beyond. Overall, the global regulatory situation is considered likely to remain generally under control in the period until 2008. The situation between 2008-2013 and beyond will be determined by a combination of factors -

- Stewardship programmes successfully ensuring, demonstrating and communicating the safety of Gramoxone under typical use in developed and developing countries
- Success in demonstrating and communicating the economic, environmental and social benefits of paraquat and its importance for the sustainable use of glyphosate products
- Success of the AWT product roll-out globally, the impact of AWT on the survival rate following ingestion and the adoption of AWT as the standard by national and international authorities.
- The outcome of the EU's 2008 interim review, and the EU's 2013 periodic review, as to whether the requirements for Annex I inclusion continue to be satisfied.
- The level of generic entry potentially limiting Syngenta's influence over paraquat regulatory strategy.
- Success in keeping paraquat out of the Rotterdam Convention on Prior Informed Consent (PIC).
- Success in containing the perceived association between paraquat and Parkinson's Disease as an academic rather than a regulatory human safety issue.
- Success in managing the development and implementation of hazard based, precautionary and comparative regulatory policies.
- Success in managing the impact of food industry protocols on paraquat use.
- The lack of emergence of a replacement active ingredient, perceived to be of lower risk.

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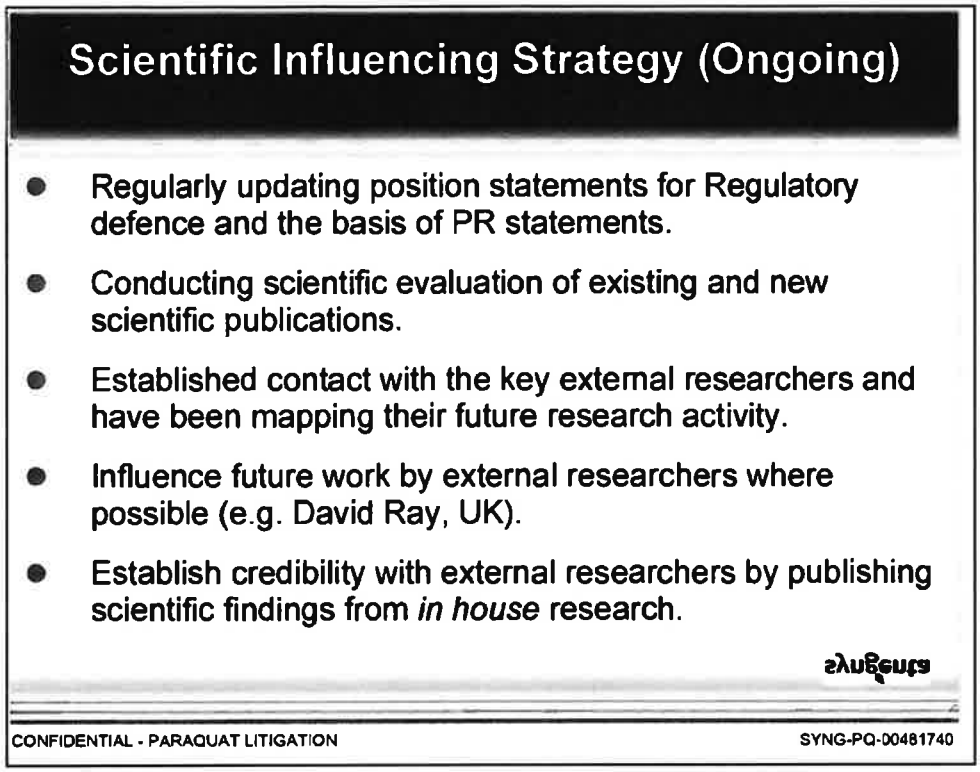
7.4. Neurotoxicity

In 1999 EPA began a phased data call-in (DCI) of acute, subchronic and developmental neurotoxicity studies. Paraquat was not a high priority but is included in later phases of the DCI. New studies pose risk of unexpected findings at doses below current reference doses. Paraquat has some structural similarity to MPTP which has been shown to induce Parkinson's Disease (PD) like symptoms in humans. Publications exist citing correlation between incidence of PD and herbicide use, including paraquat. Paraquat has markedly different properties from MPTP such that it does not readily cross the blood-brain barrier. Recent studies have focussed on the cumulative effects of pesticides, including paraquat; different developmental stages of the animal models; and development of PD hazard models, using high levels of pesticides to demonstrate changes. A high level of funding will ensure PD research will increase and focus on environmental factors such as exposure to pesticides. There are a number of wellknown PD suffers and these will ensure PD receives high media attention. Future publications may show misleading results or interpretation & it is highly likely that paraquat will continue to be drawn into the debate. The strategy is to -

- Monitor publications and presentations.
- Develop links with key researchers & PD societies to gain forward visibility and influence of further work.
- Develop capability for Syngenta to challenge key findings.
- Implement an influencing strategy to ensure that a rational risk assessment will prevail; to contain any potential impact on Gramoxone; and to shift the focus of serious PD research to other environmental factors with an exposure profile more consistent with being a PD risk factor.
- Consider appropriate timing for generation of paraquat neurotoxicity studies.

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQ-02036746

SYNG-PQ-00481718 (at 00481740)



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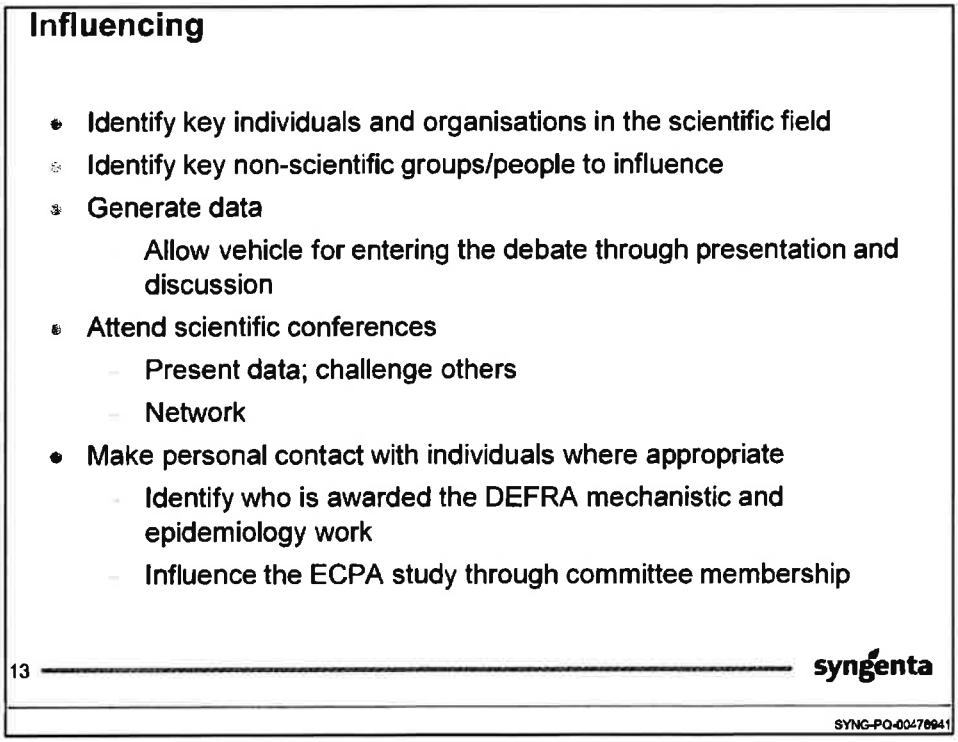
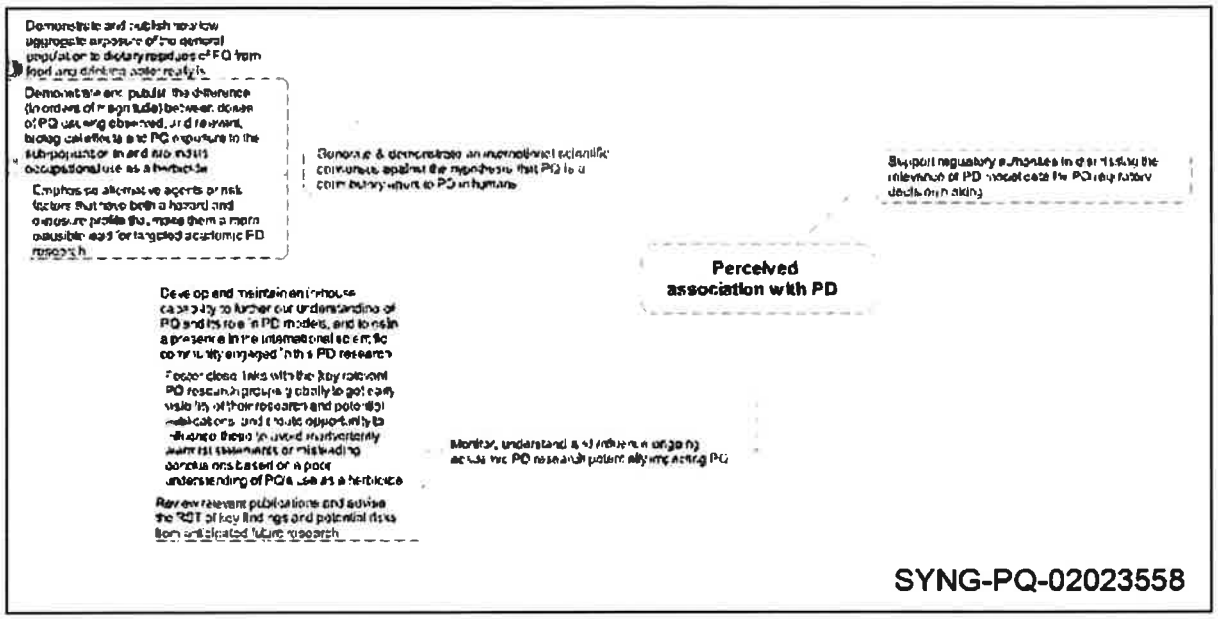
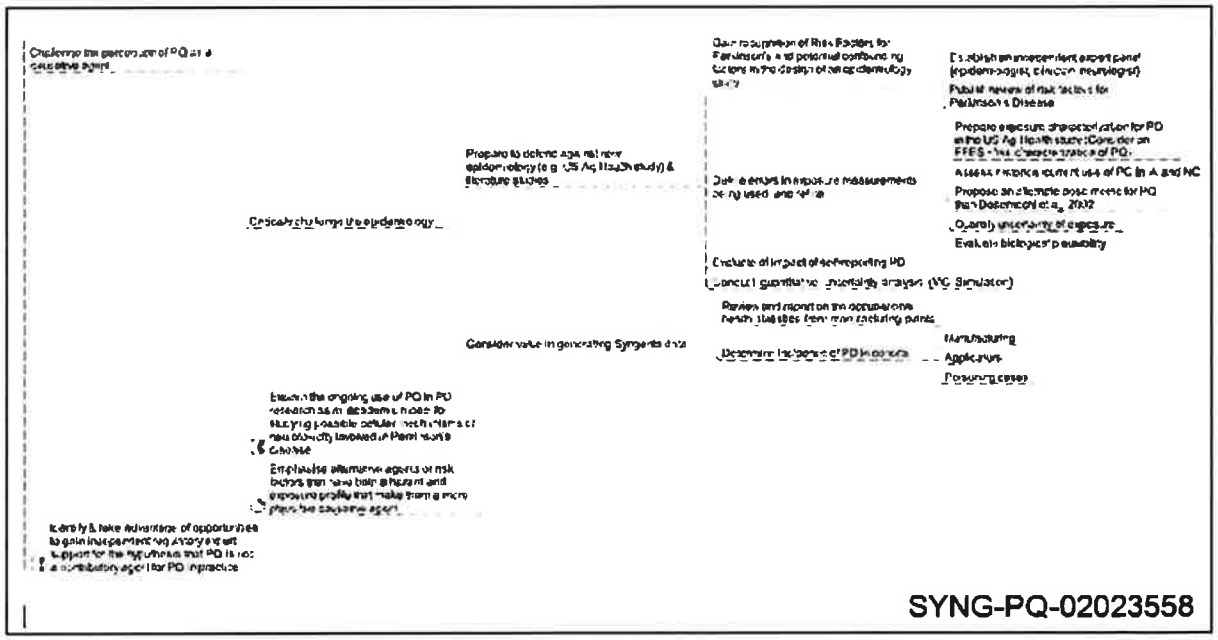


SYNG-PQ-02023558





Minutes of the 9th June 2003 PQ RDT – Regulatory science foresight – PD

Attendees –

Ian Wheals,	NSH Section Leader, Global Regulatory Affairs, Basel
Jim Markle,	Global PQ dietary exposure specialist, Greensboro, USA
David Scott,	Global Stewardship, Basel, Switzerland
Rusty Wendt,	NAFTA PQ marketing manager, Greensboro, USA
Jonathon Akins,	NAFTA Product toxicologist, Greensboro, USA
Tim Pastoor,	Health Assessment, Greensboro, USA
Sunmao Chen,	Environmental Fate, Greensboro, USA
Warner Phelps,	Environmental Fate, Greensboro, USA
Jeremy Dyson,	Global PQ environmental fate specialist, Jealotts Hill, UK
Greg Watson,	Herbicide section leader, NAFTA regulatory affairs, USA
Monty Dixon,	NAFTA operator exposure specialist, Greensboro, USA
Jeff Peters,	NAFTA PQ environmental fate specialist, Greensboro, USA
Karla Pires,	LATAM Registration Manager for PQ, Sao Paulo, Brazil
Harald Gampp,	PQ Regulatory Manager, Global Regulatory Affairs, Basel
Peter Sutton,	Ecotoxicology specialist, Jealotts Hill, UK
Chuck Foresman,	NAFTA NSH Technical Manager, Greensboro, USA
Andreas Stehli,	Global Development Project Leader, Basel, Switzerland
Jerry Wells,	NAFTA Registration Manager for PQ
Eileen Kennedy	Dietary exposure specialist, Greensboro, USA
Mike Clapp	Global Health Assessment Lead, Alderley Park, UK

Part-time by teleconference -

Nick Sturgess,	PQ neurotoxicology specialist, Alderley Park, UK
Luc Sueit,	APAC Registration Manager for PQ, Bangkok, Thailand
Diane Castle,	Head on European Regulatory Affairs, UK
Kim Travis,	Risk assessment modelling, Alderley Park, UK

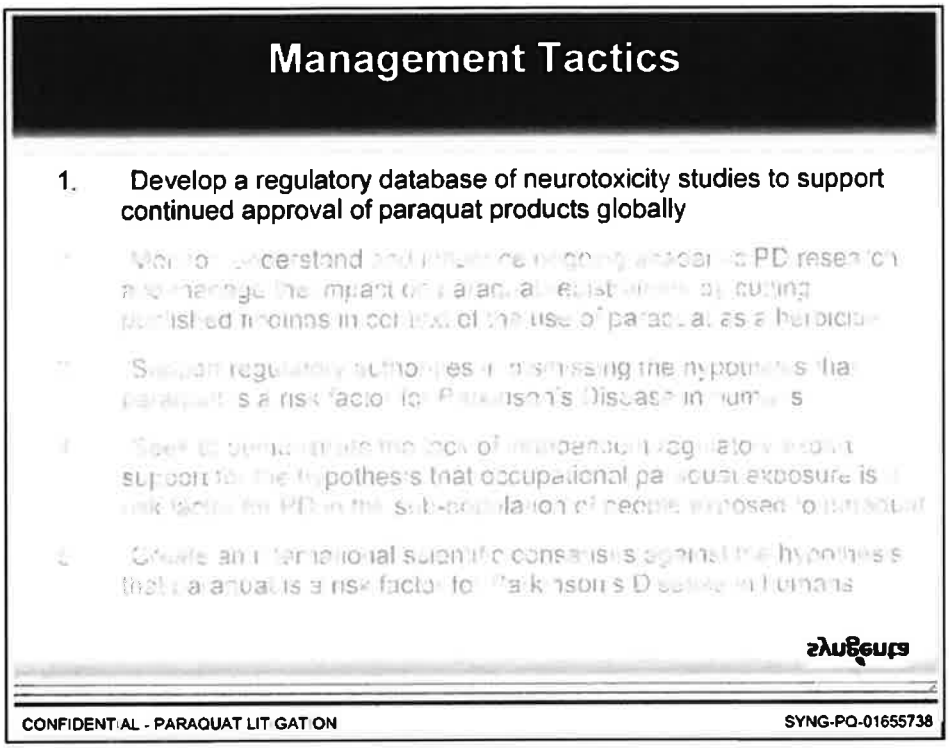
Minutes -

Ian Wheals welcomed the extended PQ regulatory development team (RDT) and explained that the emphasis of the 9th June 2003 session will be on raising the level of regulatory science foresight. The intention is to focus on the related topics of PD/neurotox hazard; operator exposure; dietary exposure; water exposure. The objective is to move from a situation where we work predominantly reactively in discrete scientific disciplines to a situation where we have a coherent strategy across all disciplines focussing on external influencing, that proactively diffuses the potential threats that we face.

The comment was made that one of the reasons for the negative image of PQ that pervades the views of many regulatory stakeholders, influencing stakeholders and the general public is the historical under-investment by Syngenta in activities to support a positive image with these stakeholders. The challenge for the RDT is to clarify to the business, the level of regulatory science investment required to meet the business's PQ

SYNG-PQ-01023454

From Techno-Regulatory Meeting 11/4/04 **SYNG-PQ-01655689** (pg. 1 and SYNG-PQ000484403 Pdf pg. 50):

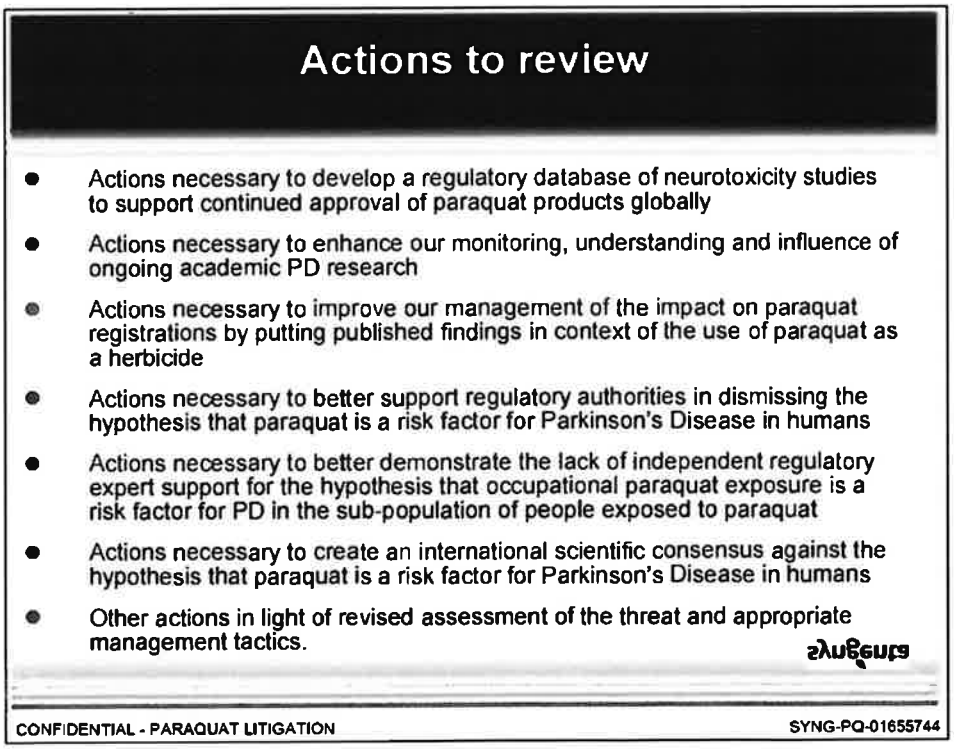


Management Tactics

1. Develop a regulatory database of neurotoxicity studies to support continued approval of paraquat products globally

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQ-01655738

PDF pg. 59:

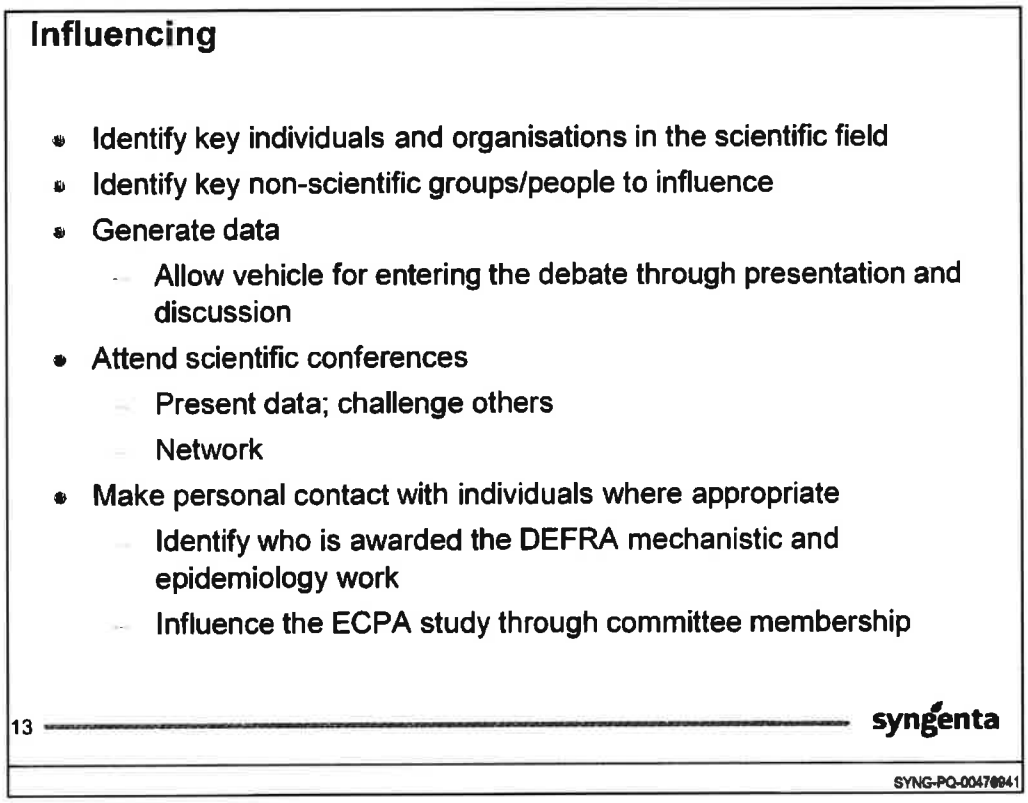


Actions to review

- Actions necessary to develop a regulatory database of neurotoxicity studies to support continued approval of paraquat products globally
- Actions necessary to enhance our monitoring, understanding and influence of ongoing academic PD research
- Actions necessary to improve our management of the impact on paraquat registrations by putting published findings in context of the use of paraquat as a herbicide
- Actions necessary to better support regulatory authorities in dismissing the hypothesis that paraquat is a risk factor for Parkinson's Disease in humans
- Actions necessary to better demonstrate the lack of independent regulatory expert support for the hypothesis that occupational paraquat exposure is a risk factor for PD in the sub-population of people exposed to paraquat
- Actions necessary to create an international scientific consensus against the hypothesis that paraquat is a risk factor for Parkinson's Disease in humans
- Other actions in light of revised assessment of the threat and appropriate management tactics.

CONFIDENTIAL - PARAQUAT LITIGATION SYNG-PQ-01655744

SYNG-PQ-00476929 (slide 13):



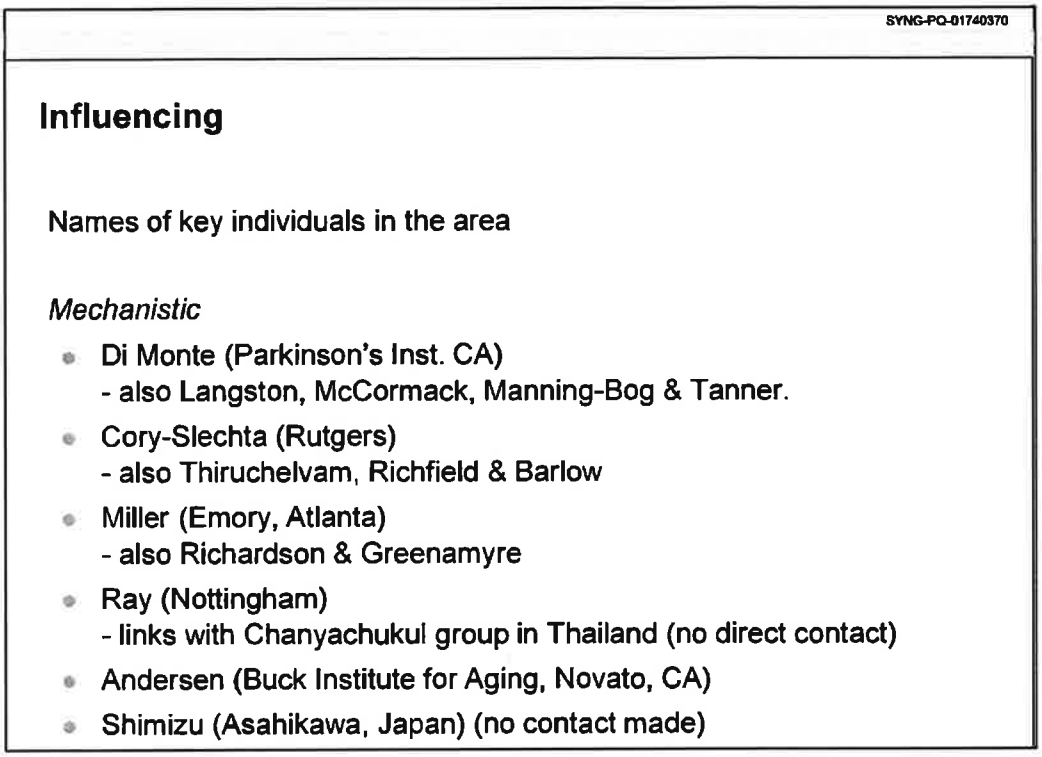
Influencing

- Identify key individuals and organisations in the scientific field
- Identify key non-scientific groups/people to influence
- Generate data
  - Allow vehicle for entering the debate through presentation and discussion
- Attend scientific conferences
  - Present data; challenge others
  - Network
- Make personal contact with individuals where appropriate
  - Identify who is awarded the DEFRA mechanistic and epidemiology work
  - Influence the ECPA study through committee membership

13 syngenta

SYNG-PQ-00476941

Slide 14:


SYNG-PQ-01740370
Influencing
Names of key individuals in the area
Mechanistic
Di Monte (Parkinson's Inst. CA)
- also Langston, McCormack, Manning-Bog & Tanner.
Cory-Slechta (Rutgers)
- also Thiruchelvam, Richfield & Barlow
Miller (Emory, Atlanta)
- also Richardson & Greenamyre
Ray (Nottingham)
- links with Chanyachukul group in Thailand (no direct contact)
Andersen (Buck Institute for Aging, Novato, CA)
Shimizu (Asahikawa, Japan) (no contact made)

Slide 15:

Influencing

Names of key individuals in the area

Epidemiology

- Tanner (Parkinson's Inst. CA) & Kamel (NIEHS, RTP) - *Farming & Movement Evaluation Study: Pesticides & PD risk in the agricultural health study.*
- Chesselet (UCLA) - *Gene environment studies in PD.*
- Chan (Sydney, Australia) - *Study of PD in Australia.*
- Ritz (UCLA) - *PD susceptibility genes & pesticides.*
- Firestone & Checkoway (Washington) - *Environment & biochemical risk factors for PD.*
- Nelson (Stanford) - *Environmental & genetic risks for PD.*
- Seaton (Aberdeen) - *Genetic, environmental & occupational risk factors for PD.*
- Greenlee (Marshfield Medical Research Foundation, Wisconsin) - *Pesticides, genetics and risk of PD.*
- Elbaz (ISERM, France) - *Case control study of PD among subjects characterised by a high prevalence of professional exposure to pesticides.*
- Louis (Columbia) - *Environmental epidemiology of essential tremor.*

Slide 16:

SYNG-PQ-01740372

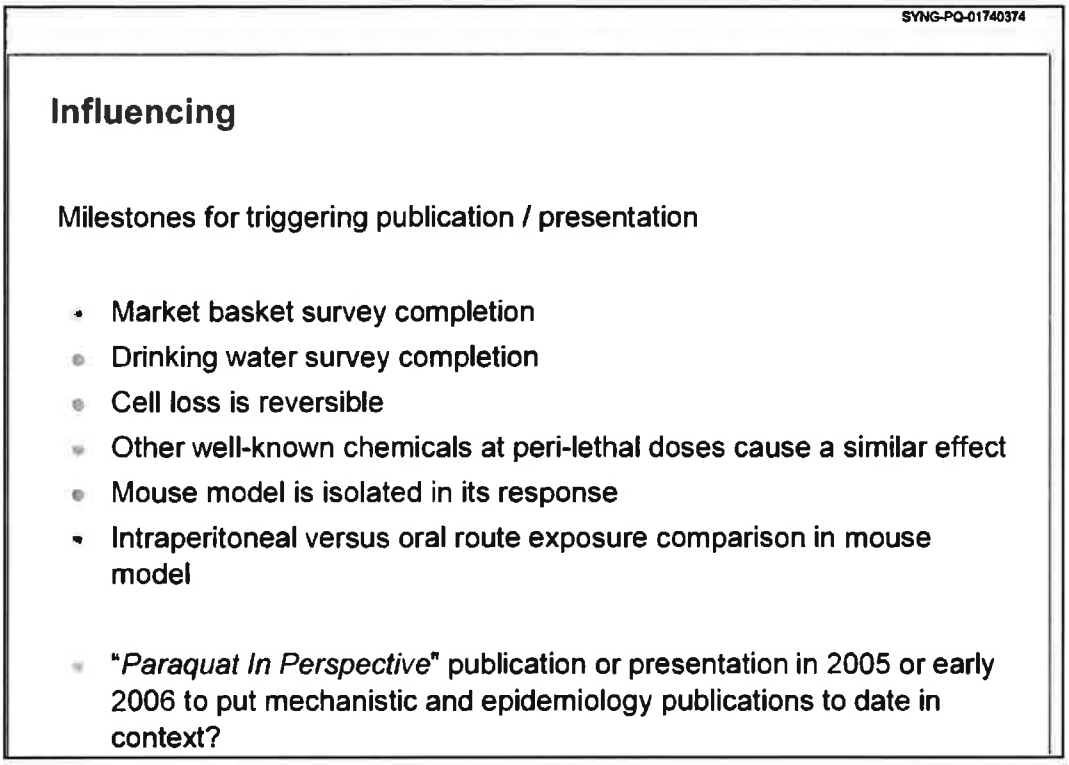
Influencing

Names of key individuals in the area

Mechanistic & Epidemiology

- Abi Li (Exponent, San Francisco)
- Ian Dewhurst (PSD, York; rapporteur for EU review)
- Paul Rumsby (MRC IEH, Leicester) - Pesticides & PD review.
- Jim O'Callaghan (CDC, WV) - MPTP expert

Slide 18:


SYNG-PQ-01740374
Influencing
Milestones for triggering publication / presentation
Market basket survey completion
Drinking water survey completion
Cell loss is reversible
Other well-known chemicals at peri-lethal doses cause a similar effect
Mouse model is isolated in its response
Intraperitoneal versus oral route exposure comparison in mouse model
"Paraquat In Perspective" publication or presentation in 2005 or early 2006 to put mechanistic and epidemiology publications to date in context?

SYNG-PQ-00474675:

Paraquat: Neurotoxicity and Parkinson's Disease

Outline of the issue -

Historically, specific acute, subchronic and developmental neurotoxicity studies have not been considered routinely necessary, or required by regulatory authorities, unless the substance was an organophosphate; inhibited cholinesterase; produced cholinergic-like toxic signs or affected morphology of the central and peripheral nervous systems. Paraquat does not affect the nervous system and as such, no specific regulatory neurotoxstudies have been undertaken.

US EPA recently decided to make acute and subchronic neurotoxicity studies a standard regulatory requirement, and in 1999 EPA began a phased data call-in (DCI) of acute, subchronic, and developmental neurotoxicity studies. Paraquat was not a high priority but is included in later phases of the DCI. Similarly in Japan, MAFF now intend to routinely request acute and subchronic neurotoxicity studies and Syngenta will be required to fill this data gap by the end of 2006 in order to support continued approval of paraquat based products in Japan.

New studies always pose potential risk of unexpected findings at doses below current reference doses.

Paraquat has some structural similarity to the chemical MPTP which has been shown to induce Parkinson's Disease (PD) like symptoms in humans, but paraquat has markedly different properties from MPTP such that it does not readily cross the blood-brain barrier. As a consequence however, some academic researchers have used paraquat as a model to develop test system to study PD and develop potential therapies. This does not imply paraquat is in any way associated with the actiology of the disease.

However, publications do exist citing correlation between incidence of PD and herbicide use, including paraquat and other academic researchers have sought to examine the effects of pesticides including paraquat on the central nervous system, and their potential to produce PD-like symptoms. Recent studies have focussed on the cumulative effects of pesticides, including paraquat; different developmental stages of the animal models; and development of PD hazard models, using high levels of pesticides to demonstrate changes.

In 2003 WHO commented on the epidemiological studies seeking to examine associations between PD and exposure to chemicals, including pesticides, "*associations with exposure to specific pesticides have not been shown consistently*". WHO also commented on the research examining the effects of pesticides including paraquat on the central nervous system, and their potential to produce PD-like symptoms, "*the design of these studies renders the relevance of these data questionable for the risk assessment of dietary exposure to paraquat residues*". The WHO expert panel concluded "*that the available mechanistic and other animal studies did not support the hypothesis that paraquat residues in food are a risk factor for Parkinson's disease in humans.*"

In contrast, some NGOs opposed to pesticides in general and paraquat in particular have claimed that paraquat is implicated as a causative or contributory agent in PD. They have and will likely continue to make this claim to regulatory authorities and the general public.

SYNG-PQ-00474675

(continued)

Minutes of the 9th June 2003 PQ RDT – Regulatory science foresight – PD

Part-time by teleconference -

Nick Sturgess,	PQ neurotoxicology specialist, Alderley Park, UK
Luc Streit,	APAC Registration Manager for PQ, Bangkok, Thailand
Diane Castle,	Head on European Regulatory Affairs. UK
Kim Travis,	Risk assessment modelling, Alderley Park, UK

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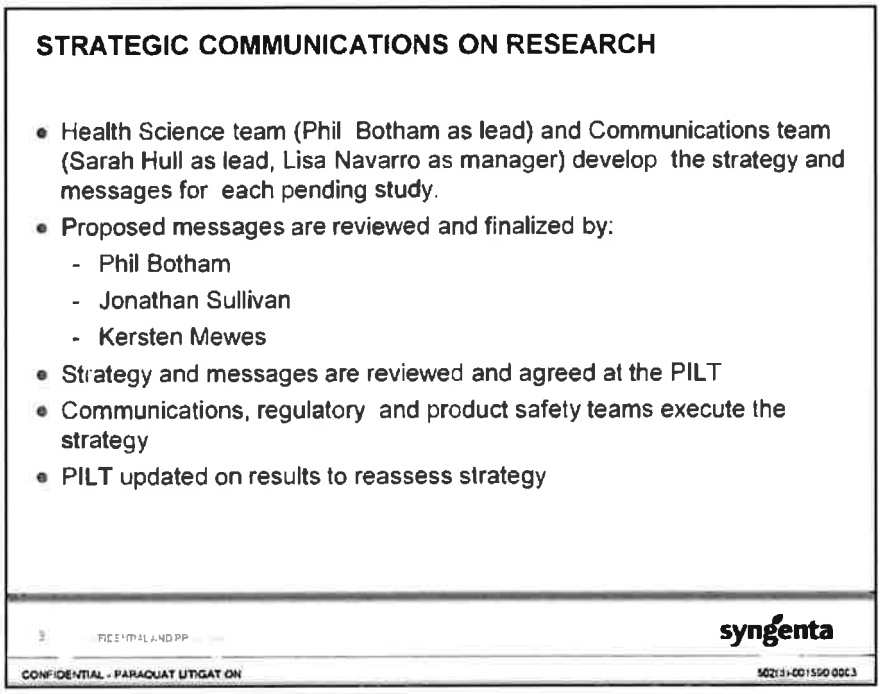
SYNG-PQ-01662351

HEALTH SCIENCE TEAM 2011

502(d)-001590.0001 March 8, 2011 Presentation:



STRATEGIC COMMUNICATIONS ON RESEARCH

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- Proposed messages are reviewed and finalized by:
  - Phil Botham
  - Jonathan Sullivan
  - Kersten Mewes
- Strategy and messages are reviewed and agreed at the PILT
- Communications, regulatory and product safety teams execute the strategy
- PILT updated on results to reassess strategy

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CONFIDENTIAL - PARAQUAT LITIGATION

SYNG-PQ-01148759:

CONFIDENTIAL

PARAQUAT HEALTH SCIENCE TEAM

MINUTES

29th June 2012, 09.00 – 16.00 BST

Present: P A Botham, C B Breckenridge, J D Sullivan, L L Smith, N C Sturgess, P Hertl, D J Minnema (via phone), K Z Travis, A R Cook, K Mewes, M Dixon (via phone), C Campbell (via phone),D J Berry, Sir Colin Berry

Apologies: R A Brown, J McFarland, A Nadel

29 June 2012 (Friday)

SYNG-PQ-01148759

	scientific opinion in order to better address the risk/benefit issue at the local level. Reference was made to the on-going activities via paraquat.com and the internal digital marketing campaign in this the fiftieth year of sales of 'Gramoxone'. The need for a program of scientific publications accompanied by presentations and advocacy at appropriate scientific meetings was highlighted as was the identification of appropriate scientific advocates who are independent of Syngenta. Measures of success would include having our publications cited in reviews, e.g. wrt. epidemiology. There is a need to identify key internal milestones in the development of our knowledge / understanding for grounding of the positions we wish to advocate. We could then inititiate specific discussions at conferences with others holding contrary views, along the lines of: there is inconsistency in the literature, what does the literature really say? What is really happening? It was recognised that there would be no ,quick win' in what would be a long and sustained process of contributing to the evolution of scientific opinion.	

SYNG-PQ-01148760

8.	**PBPK model development – status report & timelines (ppt. presentation from KZT)** KZT briefly summarised the current status of development of the PBPK model (Hamner Institute). The model is good but there is an issue over the ability to predict the long-term elimination from plasma, the terminal phase for paraquat in plasma having an apparent tendency to be under-predicted. The next step is to scale the model to man and analyze the sensitivity to this discrepancy and the fraction excreted in urine in man (59% vs 100%). A NHP urinary excretion study may be required, the meeting agreed that this should be provisionally identified to the PILT in view of the sensitivity and governance procedures likely to be required. **ACTION: PAB** to flag potential future need for NHP study to the PILT	KZT

SYNG-PQ-01148762

This is an example of meeting minutes discussing the Goldman, 2012 study:

502(D)-0118570.0001 (they reviewed Goldman 2012):

From:	Sullivan Jonathan Dale CHBS
Sent:	22 October 2012 17:06
To:	Hull Sarah USWS; Barrett Paul CHBS; Nadel Alan USGR; Mewes Kersten CHBS; Dieterle Roland Mario CHBS; Brown Richard Anthony CHBS; Botham Phil GBJH; Cook Andy GBJH
Subject:	NOTES OF PARAQUAT COMMUNICATIONS MANAGEMENT TEAM MEETING HELD ON 22 OCTOBER 2012

The Paraquat Communications Management Team (Richard Brown, Kersten Mewes, Roland Dieterle and Jonathan Sullivan in Basel and Phil Botham and Andy Cook by telephone) met on 22 October 2012 . There was no representation from Corporate Affairs .

The purpose of the meeting was to review and agree the action to be taken in relation to the publication "Genetic Modification of the Association of Paraquat and Parkinson's Disease" , by Dr Samuel Goldman of The Parkinson's Institute, et al., published online on 8 October 2012 in "Movement Disorders", and to review an advanced draft of the position statement on paraquat and Alzheimer's disease, developed by Andy Cook from the original draft produced by Paul Barrett .

The co-authors of the Goldman publication included Freya Kamel and Caroline Tanner and like the earlier publications for which they were respectively lead authors, the study reported in the publication referred to a population drawn from the Farming and Movement Evaluation (FAME) case-control study nested in the Agricultural Health Study .

The thesis of the study was that as glutathione transferases provided cellular protection against oxidative stress, homozygous deletions of genes encoding glutathione S-transferase M1 (GSTM1) or T1 (GSTT1) would increase the risk of Parkinson's disease associated with paraquat use . 50% of Caucasians lacked functional GSTM1, and 20% lacked functional GSTT1 . The analysis included 87 cases and 343 controls with complete data . 233 members of this total population had the GSTM1*0 deletion and 95 the GSTT1*0 deletion . A total of 73 subjects (all male), of whom 21 cases and 52 controls, were assessed based on interview as having used paraquat . The risk-factor-associated Odds Ratio for Parkinson's disease for paraquat use (ever versus never) among the male members of the population (63 cases, 261 controls) was 2.6, close to the Odds Ratio in the Tanner publication .

The study found (apparently without reference to paraquat use) that GSTM1*0 was associated with a significantly *reduced* PD risk (Odds Ratio 0.5 for male members of the population) . However the study reported that the Odds Ratio for Parkinson's disease among paraquat users with the GSTT1*0 was 11.1 . This finding referred to a population of 9 cases and 6 controls , the authors reporting on this basis that "results are compatible with at least a 3-fold increase in risk" . the other limitations of the study admitted by the authors were that the effects of agents other than paraquat could not be excluded; that paraquat use was determined by self-report and could be subject to misclassification ; that the inclusion of prevalent PD cases still living at AHS enrolment gave rise to the possibility of survivor bias ; and that reliance on proxy informants for a larger proportion of case subjects than control subjects (in fact 17% versus 1%) could have introduced bias .

However a "breaking news" feature prominently covering the study on the centre of the home page for The Parkinson's Institute headlined that "Strikingly, the risk of Parkinson's disease was increased 11-fold in people who had a common genetic variant (defective GSTT1 gene) and worked with Paraquat" , that "An 11-fold increased risk of Parkinson's disease is one of the largest risks ever reported" and that "Paraquat has been used for decades" , without referring to any of the limitations of the study . The Parkinson's Institute press release for the publication said that although Goldman was the lead author, the study had been carried out by Tanner and Kamel .

CONFIDENTIAL - PARAQUAT LITIGATION 502(d)-0118570.0001

In discussion of the paper the admission of the authors that paraquat was thought to be poorly metabolized and was probably not a direct substrate of GST was noted . The fact that the claimed increased risk for Parkinson's disease with paraquat use was associated with one of the two gene deficiencies but not the other was ostensibly at odds with the biological plausibility of the thesis in the paper . It could be helpful to confirm the relationship between the population in this study and the population in the Tanner 2011 publication . The fact that the study appeared to admit that some subjects had claimed to have used paraquat before 1962, when the product was launched, provided further evidence of the risk of bias .

It was agreed that :

(1) Richard Brown with Andy Cook would produce a draft holding statement and send this in the first instance by 24 October to Jonathan Sullivan for review
(2) Phil Botham would request a view from Pierluigi Nicotera on the biological plausibility of the study
(3) In addition Phil Botham would commission an external expert review by Jack Mandel of the study
(4) Consideration would be given thereafter to the value of submitting a new FOIA request for the data underlying the study
(5) A briefing would be necessary, taking into account such of the output from actions (1) to (3) as was then available, for Kersten Mewes ahead of his meeting with stakeholders in Australia on November 15 .

It was also agreed that Jonathan Sullivan would circulate the latest draft of the position statement on paraquat and Alzheimer's disease and that comments would be provided to him by October 26 .

Jonathan .

CONFIDENTIAL - PARAQUAT LITIGATION 502(d) 0118570.0002

From: Sullivan Jonathan Dale CHBS
Sent: Friday, March 18, 2011 4:57 PM
To: Hull Sarah CHBS; Mewes Kersten CHBS; Brown Richard Anthony CHBS
Cc: Botham Phil GBJH; Cook Andy GBJH
Subject: CONFIDENTIAL AND PRIVILEGED COMMUNICATION
Attachments: DB Neuroepi.pdf

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Dear All,

Attached is a notification by Andy Cook of a scientific publication which calls for a meeting of the PQ SWAT Team under the procedure agreed at the last PILT Meeting .

I will have my assistant schedule this meeting when she is back in the office on Monday .

Regards,

Jonathan .

CONFIDENTIAL - PARAQUAT LITIGATION 502(d)-0109107.0001

From: Cook Andy GBJH
Sent: Freitag, 18. März 2011 11:59
To: Sullivan Jonathan Dale CHBS
Cc: Botham Phil GBJH
Subject: CONFIDENTIAL AND PRIVILEGED COMMUNICATION

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Jonathan,

The attached publication was highlighted during one of our recent routine literature searches although the on-line publication date appears to be 24th July 2010. The authors of this epidemiology study include Gatto and Ritz.

We are flagging this study to you under the agreed process for highlighting paraquat studies to the 'SWAT' team on the basis that we believe they warrant external technical review and may require production of a Company position statement.

As part of the health science team's discussions on publication strategy we may also wish to consider whether there is any opportunity to produce a broader critical review of the approach used by Gatto / Costello / Ritz.

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- PILT updated on results to reassess strategy

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PQ SWAT TEAM (1/2)

- Purpose
  - To immediately triage the situation triggered by the release of a new study or news article
  - To determine the necessary actions and assign responsibilities to mange the matter short- and near- term
- Core team includes
  - Jonathan Sullivan, legal
    - (back-up?)
  - Sarah Hull, communications
    - Medard Schoenmaeckers, media
  - Richard Brown, stewardship
    - Lisa Navarro, issues management
  - Phil Botham, product safety
    - Andy Cook, technical support

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502(d)-0109107.0001

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Attachments:	DB Neuroepi.pdf

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I will have my assistant schedule this meeting when she is back in the office on Monday .

502(d)-0118569.0001 (Emails from Andy Cook / Peter Campbell):

From: Campbell Peter GBJH
Sent: 09 August 2013 11:27
To: Cook Andy GBJH
Subject: Paraquat publication review process

Andy
Do you have anything written down you can share with me regarding your PQ Publication response team process? I have to set something up for TMX (without the legal dimension!!) so would welcome any learnings from your area!
Regards
Peter

CONFIDENTIAL - PARAQUAT LITIGATION 502(d)-0118569.0002

Response: **502(d)-0118569.0001**

From: Cook Andy GBJH
Sent: 09 August 2013 14:26
To: Campbell Peter GBJH
Subject: RE: Paraquat publication review process
Attachments: NOTES OF PARAQUAT COMMUNICATIONS MANAGEMENT TEAM MEETING HELD ON 22 OCTOBER 2012; PARAQUAT COMMUNICATIONS MANAGEMENT TEAM MEETNG ON 12 SEPTEMBER 2012 ; PARAQUAT COMMUNICATIONS MANAGEMENT TEAM MEETING ON 22 AUGUST 2011

HI Peter,

In outline the process is as follows:

The "PQ SWAT Team" confirmed at the 8 March 2011 PILT Meeting met today to review and consider the response to the following publications (attached) :

(1) "Biochemical and Toxicological Evidence of Neurological Effects of Pesticides : The Example of Parkinson's Disease" : Moretto A. et al., Neurotoxicology, 11 March 2011
(2) "Alpha-Synuclein Gene May Interact with Environmental Factors in Increasing Risk of Parkinson's Disease" : Nicole M. Gatto et al., Neuroepidemiology, 24 July 2010
(3) "Autonomic Dysfunction in Paraquat Survivors" : Sudheera Sammanthi Jayasinghe et al. (located on www.asiatox.org) .

Before considering the publications the following process points were agreed :

(A) The team will be known as the Paraquat Communications Management Team
(B) Meetings will be convened immediately on notification of any publication requiring review . Product Safety will make the judgment as to whether any given publication is of a level of significance to trigger notification
(C) All addressees of this email will be invited to each meeting . Meetings can be held provided that one representative of each of Corporate Affairs, Legal, Regulatory, Product Safety and Stewardship / Issue Management can attend
(D) At each meeting the team will discuss the notified publications with a view to agreeing on action within the following range of options :

- Do nothing
- Create synopsis in "postcard" format
- Commission Product Safety review
- Commission external expert review
- Update Q&As on SIM / OPOV intranet site
- Produce specific Standby Statement and Q&As / key messages dealing with the publication
- Commission scientific critique for publication
- Produce proactive Media Release
- Produce materials for communication with regulators, sales force, growers and other stakeholders

(E) JDS/AN to circulate bullet action points from each meeting to all addressees of this email .

I also attach three e-mail records from these meetings (teleconferences) of the Paraquat Communications Management Team to give you a bit more of the 'flavour' of our activities.

Happy to discuss further next week if that would be helpful.

Andy

CONFIDENTIAL - PARAQUAT LITIGATION 502(d)-0118569.0001

APPENDIX B

The following statements are taken from the Fact Summary provided by counsel:

In 1969, an ICI scientist named Swann published the results of two exposure studies (field trials conducted in Malaysia in 1965 and 1967) designed to examine the average conditions of spraying by agricultural workers in the real world. The 1965 study observed the fact that workers generally wore "light clothing" due to weather conditions and that the estates on which they worked did not typically provide "more elaborate protective clothing." Swann study; Ouzts: 47-54; *see also* Patterson (June 25, 2020): 14-17.

In the 1967 study, the study subjects were divided into four groups, with one group wearing their normal clothing during the spraying process and the other three groups wearing one of the following combinations of protective equipment: boots and gloves, gloves and mask, boots and mask. Swann study; Ouzts: 47-54; Patterson (June 25, 2020): 27-28.

A small amount of paraquat was detected in every worker's urine at some point during the 12-week spraying period. Swann study; Ouzts: 47-54; Patterson (June 25, 2020): 28-29.

Another paraquat exposure study commissioned by ICI and Chevron in 1980 reported that agricultural workers in real world situations regularly come into contact with paraquat by touching contaminated spraying equipment with their bare hands. Chester and Woollen study; Ouzts: 61-65.

Paraquat residues were detected in the urine of nine out of the nineteen workers in the 1980 study. Ouzts: 65-66, 69; Patterson (June 25, 2020): 39.

In 1995, Zeneca commissioned a study of workers in pecan orchards in the U.S. to understand their exposure based on their application methods. Part of the study observed what the workers wore during spraying after being told to wear the normal attire they would use for their application methods. Slightly more than half of the workers did not wear gloves and only four wore face shields. Ouzts: 81-88.

They were not following label-recommended instructions for the use of personal protective equipment, or "PPE." Ouzts: 87.

The study report included photos of the workers taken during the study. One photo showed a man securing the lid on a paraquat container with his bare hands (no gloves); another shows a man adjusting the spray boom position under his tractor with his bare hands (no gloves); and another shows a man rinsing out a container of paraquat with his bare hands (no gloves). Ouzts: 87-90.

The study report also included written observations about worker behavior, including bare hands touching contaminated equipment; hands not being washed during the exposure period, making phone calls in the middle of spraying operations; smoking cigarettes during the exposure period; splashing paraquat onto clothing; and eating lunch while on the tractor spraying. Ouzts: 94-100.

In an occupational exposure study published in 1996, Costa Rican banana workers were observed touching contaminated equipment with their bare hands; clearing spray nozzles by blowing them out; eating, drinking, smoking and biting their nails without washing their hands; and not showering immediately after work. Ouzts: 101-03.

In a 1997 study commissioned by Zeneca of workers in Spanish citrus orchards, while the researchers noted "minor deviations" from the label recommended PPE, the workers were required as a condition of the study to wear face shields and gloves while mixing and loading paraquat. Paraquat was detected in the urine of eighteen of the twenty study subjects. Ouzts: 106-111.

In a 2007 Syngenta-sponsored study, workers were instructed to wear what they normally would during spraying operations. Two of the workers did not wear gloves; six did not wear respirators. Observations of worker behavior included paraquat splashes on worker coveralls, shoes and sprayer; windows left open in tractor cab and heavy smell inside cab; workers touching contaminated equipment with bare hands; and a worker walking onto a treated plot. Ouzts: 122-132.

Worker 102, who wore Tyvek-type coveralls, rubber gloves and a respirator while working with paraquat, showed detectable levels of paraquat in his urine. Ouzts: 136-139.

Worker 109, who wore a respirator and a working coverall while working with paraquat, showed detectable levels of paraquat in his urine. Ouzts: 138-39.

In another 2007 exposure study sponsored by Syngenta, fifteen experienced agricultural workers were observed applying paraquat according to their "habitual or typical" work practices, or "as is," and urine samples were collected pre-, during and for the 5 days post-application. Some wore gloves; others did not. Some wore boots; others wore heavy work shoes or sports shoes. "Most" wore shorts and t-shirts, leaving lower legs and forearms uncovered. Only one wore a respirator. Ouzts: 140-45.

Observations included workers touching paraquat contaminated equipment with their bare hands; workers touching their faces with contaminated gloves; paraquat splattering; workers walking onto treated weeds; workers drinking water from a bottle with contaminated gloved hand; answering a phone call while on rest during spraying. Ouzts: 145-47.

Another "as is" exposure study from 2007 sponsored by Syngenta France observed inconsistent use of PPE, with many workers not wearing gloves or respirators while handling paraquat; workers handling contaminated equipment with their bare hands; and workers spraying in front of them and walking through paraquat-treated areas. Ouzts: 149-61.

Two of the four workers who wore respiratory equipment had paraquat in their urine. Ouzts: 164-67.

Another 2007 study sponsored by Syngenta France observed inconsistent use of PPE, with many workers not wearing gloves and only one wearing a respirator while handling paraquat; workers handling contaminated equipment or weeds with their bare hands; workers spraying their boots/shoes and themselves with paraquat; one worker using a mobile phone while spraying; and several workers walking through paraquat-treated areas. Ouzts: 169-180.

Study subject No. 9, who wore respiratory equipment, gloves, boots, trousers, shirt and a Tyvek overall, had detectable levels of paraquat in his urine. Ouzts: 179-81.

In the final 2007 occupational exposure study sponsored by Syngenta France, workers were instructed to use the PPE directed on the product label, and such equipment was provided to the subjects by Syngenta. Even wearing all of the PPE required by the label, ten of the fifteen subjects tested positive for paraquat in their urine. Ouzts: 182-192.

If paraquat is in the urine, it is being excreted by the kidneys, which means it is in the blood system. Ouzts: 52-53, 65-66, 166; Patterson (June 25, 2020): 18-19, 26-27.

All of these studies show "similar" or "consistent" trends in how farmer applicators use paraquat no matter where they are located. Ouzts: 131, 147-48, 153-54, 160-61.

Chevron realized the fact that persons would not always wear the label-recommended PPE was a potential issue. Patterson (June 23, 2020): 149.

In 1965, Chevron submitted a document to the U.S. Dept. of Agriculture observing that trained paraquat sprayers in El Salvador were not wearing any "specific protective clothing" and were "normally dressed." Patterson (June 23, 2020): 150-53.

Correspondence between Chevron and ICI indicates ICI was also aware of how paraquat products were actually being used in El Salvador. Patterson (June 23, 2020): 155.

1965 correspondence between Chevron and ICI discusses a field investigation in which it was observed that the workers wore gloves and goggles only when handling

paraquat concentrate and otherwise wore their ordinary work clothing when carrying out spraying operations. Two of the four men in the study spilled concentrate on their skin of their forearms during operations. Patterson (June 23, 2020): 157-58.

Chevron knew it was a possibility that to some extent there would be some individuals who would not follow the instructions on the label regarding the use of PPE, including that users would not always be wearing gloves. Patterson (June 25, 2020): 168-69.

Chevron participated in only one exposure study during the 21 years it sold paraquat in the U.S. Patterson (June 23, 2020): 167-68.

Following three 1983 meetings of numerous ICI employees regarding efforts to increase paraquat sales in the Americas, ICI put together a document to be used as a handout to distributors to help them answer questions going forward. The Q&A section includes a question about the difference between normal use and recommended use. ICI's answer stated: "We have a responsibility to ensure that our recommendations for safe use are clearly put over on our product labels and literature; however we have to acknowledge that users will not always follow our recommendations; misuse is a problem for all products." Ouzts: 71-76.

In that same document, another question asks, "What is normal exposure?" ICI's answer was that from the Malaysian study where paraquat was applied for "long periods (up to 13 years), spraymen did not wear anything like full protective clothing: In some cases they wore virtually no clothing at all. These people did not come to any harm and their health was perfectly normal." Ouzts: 75-76