Agatha Perez
9/1/06

John D. Abbott, Ph.D.
Team Leader-Herbicides
NAFTA Regulatory Affairs
Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300

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Mr. John Jamula
Information Technology and Resource Management Division (7502P)
Office of Pesticide Programs
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., N.W.
Washington, D.C. 20460-0001

SUBJECT: Docket No. EPA-HQ-OPP-2005-0285 -- Notice of Requests to Voluntarily Cancel Certain Pesticide Registrations (71 Fed. Reg. 30919 (May 31, 2006); 70 Fed. Reg. 62112 (Oct. 28, 2005))

Dear Mr. Jamula:

Syngenta Crop Protection, Inc. (Syngenta) writes to update EPA on new scientific evidence regarding human ingestion of the Inteon formulation of paraquat that demonstrates that Inteon works as predicted and reduces human deaths following ingestion of paraquat. Syngenta also responds to comments submitted to EPA opposing the voluntary cancellation of Syngenta's non-Inteon paraquat registrations. Cancellation of Syngenta's sole remaining non-Inteon paraquat product in the United States is appropriate for the many reasons explained below, foremost of which is that the non-Inteon product is no longer manufactured for use in the United States, Syngenta has sold all of its existing stocks of the old formulation, and the safer formulation is already established in the marketplace, thus ensuring significantly greater protection of human lives. Syngenta also writes to underscore that it continues to offer access to the safer paraquat technology to other companies that obtain paraquat registrations under FIFRA to enable them to sell a safer product.

There are two new sources of information verifying the advance in human safety provided by the Inteon formulation of paraquat: (1) an observational monitoring program in Sri Lanka shows survival rates with Inteon are significantly improved, even with the sub-optimal Inteon formulation then in use in Sri Lanka; and (2) the first known person with intentional self-poisoning involving Inteon in the United States has survived, despite ingesting approximately four ounces of Inteon.

The results of the observational monitoring program of recent human paraquat poisoning incidents in Sri Lanka demonstrate a significant improvement in survival of patients ingesting

Inteon, across a range of estimated volumes, in comparison with non-Inteon paraquat. The new evidence of Inteon's safening in humans following ingestion supports the findings of canine toxicokinetic studies previously reviewed and evaluated by EPA. The toxicokinetic studies demonstrate that levels of paraquat in the blood following ingestion of Inteon are greatly reduced relative to the non-Inteon formulation, indicating significantly reduced paraquat toxicity.

Syngenta's letter also responds to comments by companies that have asked EPA to allow them to begin manufacturing the old paraquat formulation for use in the United States again – Makhteshim-Agan of North America, Inc. (MANA) and Griffin Corporation (Griffin). They disagree with EPA's approval of the safer Inteon paraquat formulation and the Biological and Economic Analysis Division's (BEAD's) findings regarding the potential benefits of the new formulation, benefits which are now confirmed by actual human experience. In their efforts to introduce their versions of the old paraquat formulation, MANA and Griffin do not address the fact that their proposed registrations would unreasonably and significantly diminish human safety, contrary to FIFRA's standard for conditional registrations in § 3(c)(7)(A). MANA and Griffin also misrepresent the effect cancellation of Syngenta's non-Inteon paraquat product will have on costs to growers, while ignoring market forces that will continue to exert control over paraquat prices.

Contrary to the assertions made by these companies, cancellation of Syngenta's non-Inteon paraquat registration will not bar generic paraquat competition. Syngenta is offering to make the safer paraquat technology available to generic registrants through tolling arrangements on commercially favorable terms. Syngenta's offer to its competitors is highly unusual but will facilitate use of the safer paraquat formulation.

Finally, this letter also addresses MANA's misstatements of the law with regard to voluntary cancellation under FIFRA. EPA is under no legal obligation to approve MANA's or Griffin's applications to register old paraquat formulations before granting Syngenta's voluntary cancellation request. EPA should proceed with the cancellation of the older and less safe paraquat product.

I. DATA IN BOTH HUMANS AND DOGS DEMONSTRATE THE SIGNIFICANT REDUCTION IN TOXICITY ACHIEVED BY INTEON PARAQUAT

A. New Human Health Data Demonstrate the Increased Safety of Inteon Paraquat

Syngenta is providing EPA with new human health data that indicate the reduced oral toxicity, demonstrated in the dog studies reviewed by EPA, reduces human fatalities following ingestion of the Inteon formulation of paraquat. Data from a Sri Lanka monitoring survey of mostly intentional ingestions of paraquat show a significant increase in human survival compared to the non-Inteon paraquat formulation, despite a suboptimal formulation of Inteon in use in Sri Lanka at the time of the survey. Additionally, in the United States, a recent incident of intentional ingestion of a large amount of Inteon shows that Inteon significantly improves human survival following ingestion.

1. A Scientific Survey Shows Increased Rate of Human Survival Following Ingestion of Inteon Paraquat

As part of an evaluation of the Inteon formulation's impact on human health and safety, scientists from academic institutions and Syngenta recently completed an analysis of data related to 586 human paraquat poisoning incidents in Sri Lanka. *See* Wilks, M.F., *et. al.*, Improvement in Survival Following Paraquat Ingestion After Introduction of a New Formation With INTEON® Technology in Sri Lanka (Abstract, Exhibit 1). The survey began as an investigation of the circumstances surrounding self-harm attempts using paraquat in Sri Lanka. Three ethical committees covering all of the participating hospitals approved the survey protocol, and an independent Scientific Advisory Board was established to oversee data collection and analysis. This independent survey was funded by Syngenta, and the survey results are currently being prepared for publication in a peer-reviewed journal. The results of this observational monitoring program were presented earlier this month at the Asia Pacific Association of Medical Toxicologists' Congress held in Sri Lanka opening August 6, 2006.

Data were collected over a 26-month period beginning in December 2003. Syngenta introduced the new Inteon formulation in Sri Lanka in October 2004 and actively removed the non-Inteon paraquat formulation from distribution. Of the paraquat ingestion cases monitored, 297 were recorded before October 2004, and 289 cases were recorded after October 2004 (195 of the latter were confirmed by plasma or urine test to have involved ingestion of the Inteon formulation). An analytical marker was added to the Inteon formulation to differentiate between Inteon and the old Syngenta standard formulation, which also included an emetic.

The monitoring data demonstrate that Inteon produces a clinically and statistically significant increase in survival. The Inteon formulation resulted in an improvement in the overall survival rate of patients from 25.6% to 35.3%. The correlation between amount ingested and survival was strong, and Inteon showed increased survival across a range of ingestion sub-groups. Moreover, patients that ingested Inteon survived longer, allowing more opportunities to receive medical treatment and thereby improving their chances of survival. *See* Abstract, Exhibit 1. These results occurred despite a separation problem with the Inteon formulation in Sri Lanka that may have hindered mixing of the safening components with the paraquat. The survey authors expect that an improved formulation without this separation problem may result in even greater reductions in oral toxicity. *See* Abstract, Exhibit 1. The U.S. Inteon formulation is such a formulation without the separation problem.

2. First Report of Inteon Ingestion in the United States Also Demonstrates Inteon's Safety Improvement

Inteon's ability to improve human survival in the U.S. was demonstrated this year by the outcome of the first reported incident in the United States since the introduction of Syngenta's Inteon formulation. As explained in the attached case report from the treating physician, Fermin Barrueto, Jr., M.D. (Exhibit 2), an individual intentionally drank a substantial volume (reported to have consumed approximately four ounces) of Gramoxone Inteon. After treatment, the individual survived and has continued to receive medical care.

Given the large amount believed to have been consumed – up to ten times a potentially lethal amount for humans of a non-Inteon paraquat formulation – the patient would have likely died had the product been a non-Inteon formulation.[1] Dr. Barrueto wrote that Inteon was a critical factor in the patient's survival. *See* Email from Dr. Fermin Barrueto (University of Maryland) to Martin Wilks (Syngenta) (July 18, 2006) (Exhibit 3). By contrast, in June, an individual who intentionally drank a large volume (exact amount unknown) of non-Inteon Gramoxone in Canada died on the same day of ingestion, as reported to EPA under FIFRA § 6(a)(2). The comparison of these recent cases offers additional support that Inteon has the ability to increase human survival, even after intentional ingestion of larger volumes.

B. Studies in Dogs Demonstrate Inteon Paraquat's Significant Reduction in Toxicity

These new human data build on the record of improved safety shown in canine studies that Syngenta submitted and EPA evaluated in registering Gramoxone Inteon. In the Data Evaluation Records of Syngenta's canine studies with Inteon, EPA's scientists found that Inteon demonstrates a decrease in acute oral toxicity of paraquat formulations in dogs, in conformance with the new safety standard set forth in Syngenta's amended paraquat technical registration.[2] The dog data indicate that the Inteon technology decreases the systemic amount of paraquat absorbed, which decreases the potential for moribidity and mortality. EPA's Data Evaluation Record for the study stated that the results showed the U.S. Gramoxone Inteon formulation "was less toxic to dogs while providing levels and a systemic dose similar to that achieved with an existing formulation (Gramoxone) [non-Inteon formulation with emetic]." *See* EPA, Paraquat Data Evaluation Record for MRID 46364510 (June 29, 2005), at 9.

Key parameters for examining blood plasma levels of paraquat following doses administered are the (i) paraquat peak plasma concentration and (ii) area under curve (AUC). Table 1 below compares these parameters and clinical effects among several canine studies of Inteon paraquat formulations, non-Inteon paraquat formulations containing emetic, and non-Inteon paraquat without emetic. Table 1 shows that plasma levels for Inteon paraquat remain low with no lethal effects even at high doses of paraquat, where much lower doses caused death in other studies.

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[1] *See* Lock EA and Wilks MF (2001). Chapter 70: Paraquat in Handbook of Pesticide Toxicology, 2nd Edition. Editor Robert Krieger. Academic Press, San Diego, CA; Pond SM et al. (1990). Manifestations and management of paraquat poisoning. Med J Australia 152 256-259; World Health Organization (1984). Environmental Health Criteria 39: Paraquat and Diquat (http://www.inchem.org/pages/ehc.html).

[2] In assessing toxicity of Inteon formulations relative to existing non-Inteon Gramoxone formulations, kinetic studies measuring the absorption of paraquat were conducted rather than lethality studies for animal welfare reasons.

Table 1. Resulting peak plasma, AUC, inappetence, body weight loss, and mortality from paraquat studies in dogs

Formulation	Dose (mg/kg paraquat ion)	Average Peak Plasma Paraquat Concentration (µg/mL)	Plasma Paraquat AUC at 24 hours (µg/mL.h)	Inappetence	Body weight loss	Mortality/ humane sacrifice	Reference
Paraquat, without emetic	10	9.6	Not reported	Not reported	Not reported	6/6	Widdop, 1977
Paraquat, without emetic	2.5 5 10 20	2.13 3.51 6.39 6.78	5.97 10.40 21.07 29.38	Yes	Yes	0/4 0/4 1/4 4/4	Cockrill and Goburdhun, 1988
Paraquat + 0.5 g/L emetic	8	2.3	15.59	No	No	0/3	Brammer 2004a
Paraquat, 2.4 g/L (equivalent) emetic	16 32 48	4.91 3.81 4.95	18.74 17.34 40.25	Yes	Yes	0/3 0/3 2/3	Swain and Heylings, 2006
Inteon US	32 64 128	1.26 1.29 2.77	4.65 3.69 7.96	No	No	0/3 0/3 0/3	Brammer 2004b
Inteon Global	8 16 32 64 128	2.57 2.00 3.07 1.90 8.21	6.94 6.38 8.51 6.62 14.60	Yes	Yes	0/3 0/3 0/3 0/3 0/3	Brammer 2004c

Figures 1 and 2 below display information from the existing database of studies on Inteon paraquat formulations, non-Inteon paraquat formulations containing emetic, and non-Inteon paraquat without emetic. Figure 1 displays toxicity, peak plasma paraquat and AUC data. For comparison purposes, the data were combined into dose level groups (*e.g.*, 8-10, 16-20, 32, 48-64 mg/kg), as some of the formulations were tested at similar but not identical dose levels. In each of the dose groupings, the U.S. Inteon formulation provides significant additional safening compared to paraquat formulations containing paraquat or paraquat plus emetic. The safening effect is most dramatic as the dose levels increase. Figure 2 plots the 24 hour plasma paraquat AUC levels in dogs based on studies performed with paraquat without emetic, paraquat with emetic, and Inteon paraquat.

Figure 1. Comparison of plasma paraquat AUC level in paraquat, paraquat + emetic and Inteon formulations

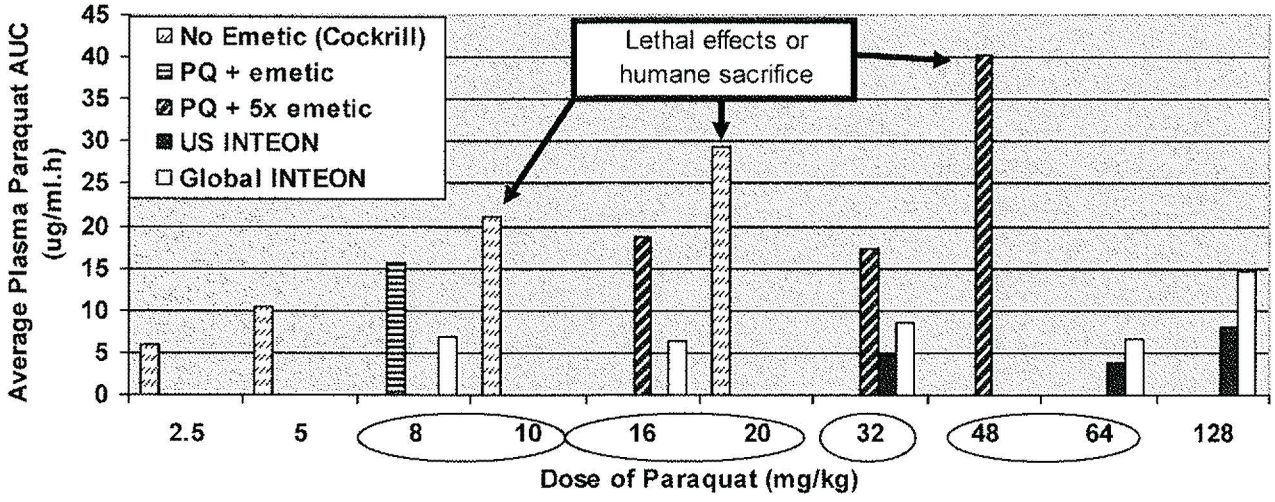
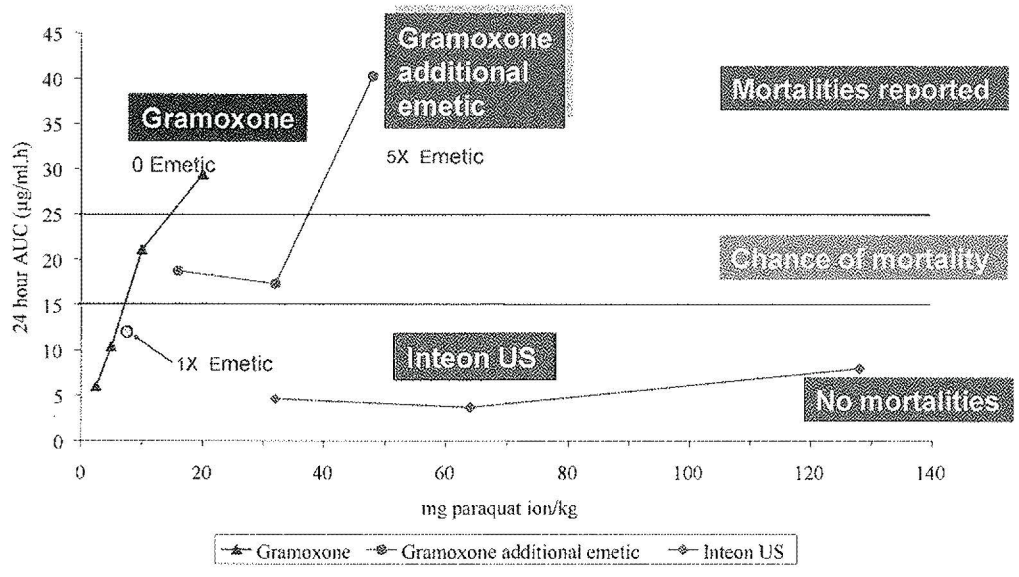


Figure 2. Comparison of 24 hour plasma paraquat AUC levels in dogs



When compared to the non-Inteon paraquat studies with and without emetic, the U.S. Inteon formulation provides a significant improvement in oral toxicity in dogs. The evidence shows that as the dose of paraquat is increased, the plasma levels of paraquat remain markedly low when Inteon paraquat is administered. Elevated emetic offered some improvement in preventing lethality, whereas lethality was not seen at doses as high as 128 mg/kg of paraquat administered from Inteon. *See* Figure 2. The canine studies provide important clinical evidence that the Inteon technology offers significant safening over non-Inteon paraquat formulations, which has now been confirmed with data from human ingestion incidents.

C. EPA Should Refine its BEAD Analysis to Reflect New Scientific Evidence

The current upper end of BEAD's December 7, 2005 estimate of the benefits of the Inteon formulation ($15.4 million) was based primarily on EPA's review of the canine studies performed on Inteon, and now is buttressed by the new scientific evidence from the human ingestion monitoring survey and incidents.[3] Also, the lower end of BEAD's estimate should be revised upward to account for the proven improvement in human survival following paraquat ingestion. BEAD stated that it was "unable to determine the number of deaths and illnesses that may be reduced by use of the formulation" and that "there is no scientific evidence that shows the new formulation would indeed affect health outcomes." BEAD Memo at 1, 3. The new scientific evidence from the human ingestion monitoring survey and incidents, as well as dog studies, confirms that Inteon significantly increases survival following ingestion of paraquat.

Human data from the Sri Lanka survey confirm that Inteon increases human survival following paraquat ingestion, even with a suboptimal Inteon formulation. Separately, the recent report of the first Inteon paraquat poisoning in the U.S. demonstrates Inteon can prevent human fatality following intentional oral ingestion of even substantial amounts of paraquat. This new evidence reinforces the conclusions of the dog studies that even as the dose of paraquat is increased, plasma levels of paraquat remain low. Inteon's reduced oral toxicity does in fact save human lives, and the lower range of BEAD's benefit estimate of "$0" can be revised. *See* BEAD Memo at 1, 8. Syngenta requests that EPA evaluate these significant data demonstrating Inteon paraquat's life-saving properties, and update the BEAD analysis to reflect these developments.

II. COMMENTS TO THE VOLUNTARY CANCELLATION DOCKET FROM MANA AND GRIFFIN FAIL TO GRASP THE BENEFITS OF INTEON AND EXAGGERATE THE COSTS OF THE NEW FORMULATION

Two paraquat applicants, MANA and Griffin, submitted comments to EPA opposing the cancellation of Syngenta registrations containing the less safe paraquat formulation. *See* EPA Docket No. EPA-HQ-OPP-2005-0285. MANA and Griffin of course were unaware of the recently released Sri Lanka survey results, but they overlook or mischaracterize other available information on Inteon's potential to significantly reduce or eliminate human deaths in the United

[3] As explained in Section II below, the upper end of Inteon's benefits will be higher ($37.88 million), given the number of accidental deaths associated with the non-Inteon formulation and their costs.

States, especially given that the Inteon formulation is now established in the marketplace and Syngenta has ceased all production and marketing of non-Inteon paraquat products.

MANA's critique of the dog studies misunderstands the Inteon technology's mechanism by attributing the reduced toxicity of Inteon solely to its increased level of emetic over that included in the old paraquat formulation. MANA's criticisms on marginal issues do not call into question the core conclusions of the canine studies. Proof of this concept in humans has now been demonstrated by the Sri Lanka monitoring program, where a significant improvement in survival following ingestion of paraquat was seen following the introduction of Inteon, even though the Inteon formulation was suboptimal and prone to separation, which compromised the ability to fully quantify the potential benefits this technology offers.

MANA also argues that BEAD overestimated the benefits of Inteon with respect to the number of fatal incidents resulting from ingestion of non-Inteon paraquat, but MANA offers no literature or data that call BEAD's methods into question. As discussed above, the scientific evidence demonstrates that Inteon will significantly improve survival following paraquat ingestion. In fact, the benefits of Inteon are even greater than BEAD estimated, when taking into account the number of human fatalities reported from 2000 to 2005, and adjusting the value of a statistical life to 2005 dollars. But even though BEAD's cost-benefit assessment underestimates the benefits of the Inteon formulation, the assessment clearly supports the cancellation of non-Inteon paraquat.

Griffin, on the other hand, chooses not to discuss Inteon's potential benefits to human health and alleges that canceling the non-Inteon paraquat registrations will shut generics out of the market and result in dramatically increased costs to growers. These assertions are baseless. Syngenta is offering to enter tolling arrangements on commercially favorable terms with companies that obtain a paraquat registration under FIFRA to make the safer technology available. Because generic companies do not typically have the same level of overhead and expenses of a research and development company such as Syngenta, it is expected that generics would be able to offer lower prices to distributors and ultimately growers and still achieve equal or greater profits than Syngenta from sales of Inteon paraquat. Therefore, any lowering of prices due to generic competition would be available if generic producers offered the safer paraquat formulation. Moreover, Griffin's and MANA's characterizations of paraquat pricing are erroneous, and they exaggerate the effects of generic competition on paraquat pricing, given market forces recognized by BEAD, such as competing active ingredients. The BEAD analysis correctly concludes that increased costs to growers resulting from use of Inteon paraquat will be minor even if the absence of generic competition were assumed, which will not be the case.

A. MANA's Comments Do Not Undercut the Conclusion that Inteon Data Show Improved Safety

MANA misapprehends the mechanism underlying Inteon's safety innovation and therefore emphasizes emesis alone as the factor in reducing paraquat toxicity. The safer Inteon formulation is the culmination of research and development by Syngenta, and consultations and input from regulatory authorities around the world. Inteon has been designed to effectively offer improved oral safening compared to previously registered paraquat formulations through a reduction in the amount of paraquat absorbed following ingestion. A key component of Inteon's

safening mechanism is a natural alginate in the formulation that rapidly gels on entrance into the low pH environment of the stomach. The alginate causes the Inteon formulation to gel in the stomach, which in turn causes the pyloric valve at the base of the stomach to constrict, holding the paraquat in the stomach and allowing the critical time needed for the emetic to reach the brain and cause vomiting. The level of emetic is increased to three times that of the previously sold Gramoxone formulations for further effectiveness.

Paraquat expelled in this manner does not reach the small intestine, where most absorption would occur, thereby minimizing exposure. A purgative, magnesium sulphate, was also added to the Inteon formulation to help purge any limited amount of product that does pass into the intestines, further minimizing exposure. While the Inteon mechanism does involve emesis, as does the older formulation, the inclusion and functioning of the alginate to gel the formulation in the stomach and allow for a more productive emesis is the key aspect of the Inteon mechanism. Data show that an increased emetic alone is inadequate to achieve the same level of safening as Inteon because paraquat that remains in a liquid state in the stomach (as opposed to a gel as in Inteon) will rapidly enter the blood and poison the body.

In support of this innovation and as a basis for registering Gramoxone Inteon, Syngenta submitted and EPA evaluated canine toxicokinetic studies, which provided data that support the new safety standard.[4] MANA tries in vain to cast doubt on the soundness of these studies, but it fails to successfully do so for the following reasons.

1. Canines Represent an Appropriate Surrogate for Assessing the Oral Toxicity of Paraquat to Humans

MANA questions the validity of data obtained from canines. In vivo animal testing, however, is the foundation for assessing human risks from pesticides and in many other branches of toxicology. In fact, in vivo animal testing is "a cornerstone of human safety evaluation," providing vital information about the toxic potential of chemical compounds.[5] Since pesticides

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[4] Brammer, A., Heylings, J., Swain, C. (2004). Paraquat 200 G/L SL Formulation (A3879D): Toxicokinetic study in the dog. Central Toxicology Laboratory. September 8, 2004. MRID 46364511; Brammer, A., Heylings, J., Swain, C. (2004). Paraquat 200 G/L SL Formulation: Toxicokinetic study in the dog. Central Toxicology Laboratory. January 28, 2004. MRID 46364518; Brammer, A., Heylings, J., Swain, C. (2004). Paraquat 240 G/L SL Formulation (A7813K): Toxicokinetic study in the dog. Central Toxicology Laboratory. September 8, 2004. MRID 46364510; Brammer, A. (2004). Paraquat 200 G/L SL Formulation (A3879BU): Toxicokinetic study in the dog. Central Toxicology Laboratory. January 7, 2004. MRID 46364517.

[5] National Research Council of the National Academy of Sciences, Intentional Human Dosing Studies for EPA Regulatory Purposes Scientific and Ethical Issues (2004), at 160-161. Data from animal models have widespread use in regulatory risk assessment, and many, if not most, toxicity standards are derived from such assessments. National Research Council of the National Academy of Sciences, Science and Judgment in Risk Assessment, (1994), at 56; *see also* EPA, Risk Benefit Balancing Under FIFRA (1991).

are not generally tested on humans, EPA's pesticide testing regime has always relied on animal studies as surrogates for varying degrees of human exposure. For these reasons, EPA explicitly requires animal toxicity testing, including the testing of canines, prior to the approval of pesticides. *See, e.g.*, 40 C.F.R. § 158.340(b)(9)(ii)(C) (requiring a "chronic nonrodent (*i.e.*, dog) feeding study"); *see generally* EPA, Risk Characterization Handbook (2000).

MANA does not offer any literature or data to suggest that controlled dog studies are not the best testing protocol for an evaluation of paraquat's oral toxicity. MANA simply notes that human ingestion will involve variable doses, which only underscores the value of these studies that measure the effects of Inteon against non-Inteon paraquat formulations in a laboratory setting. The specific choice of the canine as a surrogate for human toxicity testing reflects solid scientific principles and practice, as demonstrated in the accompanying Declaration of Sir Colin Berry, M.D., Ph.D., a pathologist and toxicologist who currently is Professor Emeritus of Pathology at Queen Mary, University of London (Berry Declaration, Exhibit 4). As Professor Berry explains, the canine is the appropriate higher mammalian species for the purpose of toxicological evaluation, possessing the digestive attributes (including the vomit reflex) necessary to generate reliable data for human comparison. Berry Declaration at 2, Exhibit 4.

The main advantages of the canine model for assessing the human toxicity of Inteon formulations are:

(1) similarity in the gastro-intestinal (GI) tract and stomach pH,

(2) an ability to vomit, and

(3) an ability to respond to the centrally acting emetic used in paraquat formulations.

Berry Declaration at 2-3, Exhibit 4.

Figure 3. **Variations in the type and distribution of gastric lining tissue in different mammals. The dog and human are closest in structure of stomach tissue. (Stomachs are not drawn to scale).**

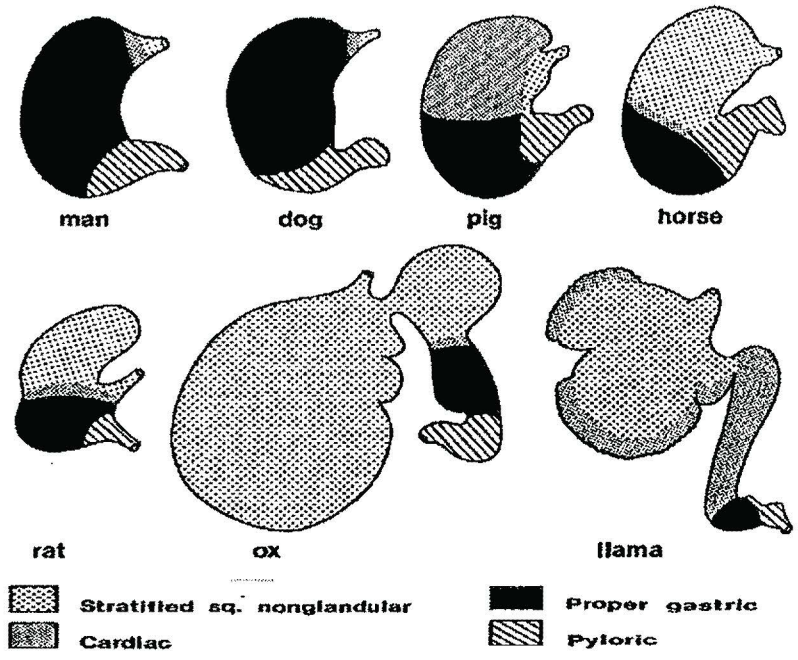

Figure 4.

Human: Dog – Comparison of GI Anatomy and Physiology

	Characteristic	Human	Dog
Relevant Similarities	Chamber	Single/glandular	Single/glandular
	Capacity	1-1.6 L	~2 L
	pH fasted	1.4 – 2.1	1.5
	Gastric Mucosa	Predominantly "Proper Gastric" (see diagrams)	
	Emptying rates	1-2 hrs	1-2 hrs
	Proportional GI lengths (%): Small	80	85
	Cecum	3	2
	Colon	17	13
	Vomit	Initiated by local irritation and/or similar neural reflex pathways to/from CNS	
Potentially Relevant Differences	Total GI Transit Time	8 – 72 hrs	6 – 8 hrs
	Small Intest. Transit	3-4 hrs	>4 to <8 hrs

From: Karadi, TT (1995). Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. Biopharm & Drug Disp. 16: 351-380.

These analogous characteristics of the dog and human have been compared and fully support the dog being an appropriate surrogate for use in toxicokinetic studies to reach a

determination of human responses to ingestion of Inteon formulations. *See* Figures 3, 4. As the process by which compounds are absorbed, distributed, metabolized, and eliminated by the canine closely resembles the same process in humans, there is no anatomical or physiological reason why human vomiting should be any less effective than canine vomiting in reducing paraquat exposure and improving survival from ingestion events.

2. Capsule Dosing Accurately Relates to Oral Ingestion

MANA seems to suggest that capsule dosing in the canine studies somehow is inadequate because humans ingest paraquat by drinking it in a liquid form. Again, MANA offers no literature or data to support its claim.

The main site of absorption of paraquat is the small intestine. When human ingestion occurs by drinking a paraquat product, the paraquat formulation is quickly transferred to the stomach, and it is at the stomach where prevention of further movement into the small intestine must take place. The canine studies provided doses of paraquat to the stomach via capsule, prior to movement into the small intestine, and thereby allow for appropriate analysis of systemic paraquat absorption.

3. The Canine Data Do Not Suggest Any Increased Toxicity Associated With Inteon Paraquat

MANA grasps at a finding of a small lung lesion observed in one dog in the U.S. Inteon formulation study and one dog in the Global Inteon formulation study, two weeks after receiving the highest dose of Inteon paraquat, and conflates this to allege that U.S. Inteon is more toxic than the non-Inteon paraquat formulation. As noted in EPA's assessment, each dog received the highest dose of Inteon formulation and only one showed a small, non-progressive lung lesion when examined after the conclusion of each study. *See* EPA, Paraquat Data Evaluation Record for MRID 46364510 (June 29, 2005) at 3, 5; EPA, Paraquat Data Evaluation Record for MRID 46364517 (July 5, 2005) at 5, 7. The lungs of those dogs receiving non-Inteon formulations were not examined for histopathology for a comparison. In any event, the lesion was observed approximately two weeks after each dog had received the last dose of formulation, and the lesion was considered neither life-threatening nor progressive. Each dog was considered to be clinically normal.

The studies provide clear evidence of Inteon's reduced toxicity, and certainly indicate no risk of increased toxicity. Unquestionably, at the highest dose level of Inteon paraquat ingested, all six dogs would have died had they ingested a non-Inteon formulation. *See* Figure 2.

4. Plasma Levels Demonstrate that Less Paraquat is Absorbed from Inteon Than Other Paraquat Formulations Across the Dose Range

MANA asserts that the absorption rate of Inteon paraquat is not related to the dose administered and that this observation raises questions about the safety of Inteon at high doses. While EPA recognized that the absorption rate increases as the dose administered increases, it also recognized that a substantially higher dose of Inteon resulted in plasma levels of paraquat similar to those from a much lower dose of the older formulation. *See* EPA, Paraquat Data Evaluation Record for MRID 46364510 (June 29, 2005) at 7-9. The key parameters directly

related to the amount of absorption are the paraquat peak plasma level and the 24 hour area under the curve for paraquat. These data are shown in Figures 1 and 2 and demonstrate a clear and positive dose response. The data on paraquat plasma parameters show that the Inteon formulation delivers significant reduction in toxicity over a wide dose range. *See* Table 1.

Furthermore, the benefit of Inteon over a range of doses in humans is confirmed in the observational monitoring survey data from Sri Lanka, where Inteon had a beneficial effect on survival following ingestion of paraquat formulations, even with a suboptimal Inteon formulation, compared with a non-Inteon formulation. *See* Abstract, Exhibit 1.

5. MANA Misunderstands the Role of the Emetic in Inteon Paraquat

The pivotal advantage of Inteon paraquat is not the ability of higher doses of the emetic to be absorbed, as MANA contends, but rather the gelling of the formulation in the stomach, preventing absorption while giving time for the emetic to take effect. As described above, the key element of the Inteon formulation is a natural alginate that gels when it enters the low pH of the stomach. The alginate causes the Inteon formulation to gel in the stomach, preventing it from entering the small intestine, where paraquat would be rapidly absorbed. Holding paraquat in the stomach, the gelling mechanism gives the emetic time to take effect and cause vomiting. As mentioned above, data show that an increased emetic alone, without the gelling technology, is inadequate to prevent paraquat absorption because paraquat that remains in a liquid state will enter the blood quickly and poison the body.

6. The Concentration of Emetic Used in Inteon Paraquat is Not Toxic

In its critique of the canine studies, MANA argues that the increased level of emetic in Inteon may be toxic. MANA is incorrect. The emetic used in Inteon has been safely used with paraquat since the 1980s. Last year, EPA increased the amount of the emetic that can be used in paraquat formulations while still exempting the emetic from the requirement of a tolerance; the Inteon formulation contains only one-half the level approved for use by EPA. When EPA first issued the exemption from a tolerance for the emetic, it stated:

> This exemption is justified because the severe health hazard associated with oral ingestion of paraquat allows for efforts to advance any opportunity to reduce retention of accidentally ingested paraquat formulations. Also, any possible adverse effect of PP796 (the inert emetic) is minimal in comparison to the irreversible severe consequences of paraquat ingestion. Based on the above information, and review of its use, it has been found that, when used in accordance with good agricultural practices, this ingredient is useful and does not pose a hazard to humans or to the environment.

EPA, Proposed Exemption for the Requirement of a Tolerance, 46 Fed. Reg. 55725 (Nov. 12, 1981). EPA reaffirmed those benefits in 2005 when it increased the amount of emetic that can be used in a paraquat formulation. *See* EPA, Exemption from the Requirement of a Tolerance, 70 Fed. Reg. 46428, 46429 (Aug. 10, 2005).

MANA questions the toxicity profile of the emetic used in Inteon paraquat, but provides no evidence to suggest that the emetic is anything other than safe. Syngenta submitted a

substantial amount of data that support the tolerance exemption for the emetic used in Inteon paraquat, including acute toxicity, genotoxicity, developmental toxicity, subchronic toxicity, and animal metabolism data. *See* EPA, Notice of Filing a Pesticide Petition to Amend the Existing Tolerance Exemption, 70 Fed. Reg. 37847, 37849-50 (June 30, 2005). There is no evidence that the emetic is toxic at the level approved by EPA, and the amount of emetic formulated with Inteon paraquat is 1.5 g/L, only one-half the level EPA approved for use.

B. Contrary to MANA's Comments, the BEAD Assessment Is Sound and May Underestimate the Number of Ingestion Incidents for the Non-Inteon Paraquat Formulation and Their Associated Costs

MANA argues that the BEAD assessment overestimates the benefits of the Inteon formulation by overestimating the number of accidental deaths caused by non-Inteon paraquat. MANA's criticisms are based on speculation, and MANA offers no evidence to counter BEAD's assumptions. Given the scientific evidence regarding reduction of fatalities discussed above, the benefits of the Inteon formulation clearly outweigh its costs. Moreover, based on more recent reports of actual incidents submitted to EPA, the BEAD assessment underestimates the number of non-Inteon paraquat ingestion incidents that occur each year. When accounting for the number of cases actually reported, and adjusting the value of a statistical life for inflation, the benefits of the Inteon formulation are likely considerably greater than estimated by BEAD.

1. The Number of Reported Paraquat Incidents Is Greater than Reflected in the BEAD Assessment

The number of incidents BEAD uses in its analysis likely is underestimated. BEAD's assessment does not take into account the significantly higher average annual number of deaths associated with accidental paraquat ingestion reported by PROSAR between 2000 and 2005, or any of the number of deaths from intentional ingestion also likely to be prevented by Inteon. Over the six-year period between 2000 and 2005, the poison control center PROSAR has reported 29 cases of paraquat poisoning in the United States. Eleven of these cases were classified as intentional and resulted in ten fatalities, while 16 were cases of accidental ingestion resulting in eight fatalities. Two additional accidental cases of reported paraquat poisoning over this time period were a result of predominantly topical exposure. Incidents of accidental ingestion between 2000 and 2005 alone resulted in an average of 1.3 deaths per year.[6] Using the adjustment applied by BEAD to account for under-reporting and coverage limitations, an estimated 5.9 unintentional deaths per year can be associated with paraquat ingestion over this six-year period. Applying BEAD's $6.42 estimated VSL, the accidental deaths that will be avoided through use of Inteon value $37.88 million each year.

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[6] MANA argues that BEAD overestimates the number of paraquat ingestion incidents because MANA disagrees with the factor EPA applies to account for underreporting. But MANA cites no literature or data refuting EPA's use of this documented factor to estimate pesticide poisonings in the U.S.

2. The Benefits of Inteon Are Underestimated When the Value of Statistical Life Is Adjusted for Inflation by EPA's Own Method

The BEAD assessment may also undervalue the benefit of the Inteon formulation. Notably, the $6.42 million VSL estimate assigned in the BEAD assessment is lower than both the "central estimate" recommended by EPA guidance and the mean VSL in the Kochi study referenced in the BEAD analysis. *See* EPA, Guidelines for Preparing Economic Analyses, EPA 240-R-00-0003 (Sept. 2000) (EPA Guidelines) at 90; Kochi and R. Kramer, An Empirical Bayes Approach to Combining Estimates of the Value of a Statistical Life for Environmental Policy Analysis, in Economic Valuation of Mortality Risk Reduction: Assessing the State of the Art for Policy Applications at 1, 3 (U.S. EPA Workshop Proceedings, 2001).

In EPA's Guidelines for Preparing Economic Analyses, EPA recommends a "central estimate" of $4.8 million in 1990 dollars, adjusted to the base year of analysis – $7.17 million in 2005 dollars. The Kochi study determined a mean VSL estimate of $6.3 million in year-2000 dollars. Adjusted for inflation, this equates to a VSL of $7.15 million in year-2005 dollars. Using the Kochi VSL estimate, upon which the BEAD assessment appears to rely, the value of saving 5.9 unintentional deaths each year, in 2005 dollars, would be $42.185 million.[7]

C. The Safer Paraquat Has Not and Will Not Lead to Significant Price Increases for Growers

Inteon paraquat provides the same effective weed control that growers have come to expect from paraquat and has proven itself in the marketplace since its introduction in late 2005. Since its registration in the U.S. four decades ago, paraquat has been an important tool for weed control in the U.S. and around the world. Growers use paraquat to control emerged weeds prior to sowing, as a directed spray between crop rows and as a harvest aid to desiccate mature crop plants to facilitate harvest. In the U.S., it is used in over 100 crops and in certain non-crop areas. Paraquat provides several environmental benefits important to farmers. It is the fastest acting contact herbicide, making it ideal for no-till farming as a preplant burndown treatment. It is not systemic, which means that it preserves weed root systems, minimizing soil erosion and reducing crop injury risk when sprays are directed in a crop. Additionally, because paraquat is tightly bound upon soil contact, it does not affect rotational crops, and the chance for leaching into water is extremely low.

The new, safer formulation of paraquat provides the same weed control and environmental benefits to growers with an increased cost of only approximately 5%. Both MANA and Griffin speculate that the costs to growers will be greater than those included in BEAD's assessment. These claims are based on the erroneous assumptions that canceling Syngenta's non-Inteon paraquat registration will prevent generic products containing the safer

[7] In addition, the mortality induced by paraquat is nearly immediate; EPA guidance notes that reducing the risk of an immediate health effect may be more valued than reducing the risk of a health effect that is less certain or manifests only after a long latency period. EPA Guidelines at 92.

formulation from entering the market and that Syngenta will dramatically increase paraquat prices. As discussed below, both assumptions have no basis in fact.

1. Canceling Non-Inteon Paraquat Registrations Will Not Keep Generic Paraquat Products Containing the Safer Technology Out of the Market

Despite the clear data on Inteon safety and the factors that restrain paraquat prices in today's market, Griffin attributes Syngenta's introduction of Inteon to a "post-patent, monopoly-protection strategy." To the contrary, Syngenta's large investment in Inteon (with no guarantee of return) and its proven success in saving lives demonstrate Syngenta's commitment to product stewardship and continued improvement in the safety of paraquat. In light of the potential to significantly impact the number of fatalities from accidental ingestion of paraquat, Syngenta has publicly offered to make the safer technology available, through tolling arrangements on commercially favorable terms, to companies that gain a registration to sell paraquat under FIFRA, but have not identified their own, alternate routes to ensuring safety at the new level.

Syngenta has taken this unusual step to facilitate the new technology's availability, even though Syngenta's innovation is protected by patent. Syngenta believes that its proposed terms for offering tolling arrangements are fair and reasonable; they are offered at a price less than what a company such as Syngenta typically could obtain in comparable situations with a proprietary product. Based on Syngenta's experience in the pesticide industry, it is confident that the proposed terms would allow generic companies that sell paraquat products containing the safer formulation to realize a net profit similar to or higher than that realized by Syngenta on its sales of Inteon products even if the generic companies chose to offer their products at lower prices than those offered by Syngenta.

Contrary to MANA's and Griffin's predictions, canceling Syngenta's non-Inteon paraquat registration will not prevent generic competition in the paraquat market. Instead, canceling the sole remaining non-Inteon registration will facilitate making a proven safer paraquat product available in the United States, while still potentially offering growers a choice among different brands of the safer formulation.

2. MANA and Griffin Misrepresent the Market Factors That Determine Paraquat Pricing

The BEAD Assessment accurately states that the new Inteon formulation will increase the cost of paraquat supplied by Syngenta to growers by approximately 5%. BEAD Memo at 4. Since the introduction of Inteon in late 2005, and into 2006, as Inteon has almost completely replaced prior paraquat formulations in the channels of trade, the list price to distributors has

increased by exactly 5%.[8] BEAD concluded that such "increases in cost as a percentage of the total operating cost per acre are minor and those increases would not likely influence a grower's decision to purchase paraquat or another herbicide." *Id.* This sentiment is echoed by the support EPA has received from numerous interested grower groups to cancel non-Inteon formulations, including the Agribusiness Association of Iowa; the Kentucky Corn Growers Association; the Oklahoma Agribusiness Retailers Association; the Texas Agri-Women; and the Wisconsin Fertilizer and Chemical Association. *See* EPA Docket No. EPA-HQ-OPP-2005-0285. Moreover, Inteon will remain reasonably priced due to the simple fact, well-known in the agricultural community, that glyphosate is the dominant non-selective herbicide and now imposes a relentless downward pressure on paraquat and other herbicide product prices.

Both MANA and Griffin ignore these fundamentals and mischaracterize historical data regarding paraquat prices. Furthermore, their arguments are premised on the assumption that there will be no generic competition if the old paraquat formulations are cancelled. In fact, Syngenta has offered to make the safer technology available to the generic producers, and, therefore, any price impact from generic competition will take place. Griffin's remarkable assertion at page 5 of its comments that the price of paraquat increased by 67 percent following Griffin's withdrawal from the paraquat market in 2003 is baseless. Syngenta's published list price for a gallon of its Gramoxone Max, Syngenta's major paraquat product, between 2002 and 2005 shows an increase of approximately six percent in cost to distributors since 2003. In fact, the cost to growers of a pound of paraquat (sold as Gramoxone Max) active ingredient between 1999 and 2005 has fluctuated within only a four percent range – and in 2005 actually reflected a 2.3 percent reduction from 1999 costs – despite both the entry and subsequent withdrawal of Griffin's paraquat registration within that time period. *See* Doane's AgroTrak (1999-2005).

Paraquat prices are determined by a variety of market forces, including competition from other active ingredients, such as glyphosate, in the burndown, non-selective herbicide market. *See* BEAD Memo at 3 (recognizing that several active ingredients are available in various paraquat markets). The effect of glyphosate competition on paraquat and other pesticides is well documented. *See* CropLife Foundation, Pesticide Use in U.S. Crop Production: 2002 (Feb. 2006), at 7, 14-16 (Table 2B). The 2.9 million pound reduction in paraquat application to cotton and soybeans between 1997 and 2002 is largely attributed to increased sales of glyphosate. *Id.* at 7. Glyphosate, paraquat's dominant competitor in the burndown, non-selective herbicide market, imposes a significant constraint to any of the paraquat price increases speculated on by MANA and Griffin.

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[8] In 2006, Syngenta's list price for Inteon paraquat to distributors is $24.44 for two pounds of active ingredient per gallon. Due to the additional volume of the alginate, purgative, and increased amount of emetic, Gramoxone Inteon contains 2 pounds active ingredient per gallon, instead of the three pounds active ingredient per gallon in Syngenta's non-Inteon product, Gramoxone Max. If Gramoxone Inteon were sold at the same volume as Syngenta's non-Inteon formulation (three pounds of active ingredient per gallon), its list price would be $36.66, which is five percent higher than the 2005 list price for non-Inteon paraquat, $34.92. Syngenta offers discounts and rebates off its list prices to its distribution partners that then affect the price actually charged to growers.

MANA's and Griffin's assertion that canceling Syngenta's non-Inteon paraquat registration will result in price increases beyond the estimated 5% is unfounded, considering historical paraquat pricing as well as market forces that influence paraquat prices.

3. Use of Inteon Paraquat Will Result in Minimal Increased Cost to Growers, As BEAD Accurately Concludes

In making its own calculations to refute BEAD's conclusions, MANA mixes prices and pesticide application figures from different years to try to show that BEAD underestimated the costs to growers. Using the figures consistently, however, BEAD's assessment of costs appears to be accurate. MANA selects Croplife Foundation's report of 4 million pounds of paraquat applied in 2002. Syngenta's published list price of Gramoxone Max in 2002 was $32.75 per gallon. Therefore, assuming 4 million pounds were applied, the total cost in 2002 was $43.7 million.[9] A 5% increase in list price would result in an increase of about $2.18 million, which is within BEAD's range of $1.8 to $2.3 million. If the same calculation is made using the cost to growers instead of Syngenta's list price, the total cost in 2002 would be $51.16 million. *See* Doane's AgroTrak (2002) (cost to growers of Gramoxone Max estimated as $38.37 per gallon).[10] A 5% increase in price to growers would result in an increase of $2.6 million, slightly above BEAD's estimate, but far below MANA's inflated and misleading calculations. The BEAD analysis correctly concludes that increased costs resulting from use of Inteon paraquat will be minor.

III. EPA SHOULD CANCEL SYNGENTA'S REGISTRATION OF THE OLD PARAQUAT FORMULATION WITHOUT REGARD TO OTHER APPLICATIONS

For all the reasons stated above, EPA should grant Syngenta's request to voluntarily cancel Syngenta's registration of the old paraquat formulation. The safer formulation is already established in the marketplace; Syngenta has sold all of its existing stocks of the old formulation; and Syngenta is offering access to the safer technology to other paraquat registrants, which will ensure availability of a safer paraquat product in the U.S.

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[9] Gramoxone Max is the sole Syngenta non-Inteon paraquat product remaining on EPA's books; Syngenta has ceased manufacturing and selling Gramoxone Max.; Gramoxone Max contained 3 pounds per gallon, not 2.5 pounds per gallon as MANA used in its calculations. BEAD recognized that Gramoxone Max contained 3 pounds active ingredient per gallon. *See* BEAD Memo at 3.

[10] CropLife Foundation's figure for total pounds of paraquat applied in 2002 appears to include the variety of paraquat products that were on the market in 2002, including Gramoxone Max and several others. CropLife Foundation's report, however, does not discuss prices to growers for these products. Doane's AgroTrak (2002) indicates that about 3.6 million pounds of paraquat were applied in 2002, and the average price to growers (among the several available paraquat products) was $12.69 per pound. The total cost to growers in 2002 would have been about $46 million, and a 5% increase would be $2.3 million, which is within EPA's estimated range of the increased cost to growers resulting from the move to the safer Inteon paraquat.

MANA misstates the law with regard to voluntary cancellation under FIFRA, and its comments fall short of articulating a legitimate reason for EPA to delay granting Syngenta's cancellation request. EPA is under no obligation to approve applications to register old paraquat formulations before granting Syngenta's voluntary cancellation request. To the contrary, FIFRA authorizes EPA to "approve or deny" a request for voluntary cancellation, subject only to the registration transfer provisions of FIFRA § 6(f)(3)(B), which accommodate users of registrations for minor uses. *See* FIFRA § 6(f)(1(D). The legislative history behind FIFRA's voluntary cancellation provisions reflects Congress' concern that minor agricultural use pesticides not be cancelled solely because of registrants' economic considerations. As a result, Congress required EPA to follow certain procedures to ensure that minor-crop users are on notice of voluntary cancellation requests and to allow such users the opportunity to take over a registration to ensure the continued availability of a safe minor-use pesticide.[11] *See* 136 Cong. Rec. S5982 (May 10, 1990) (Exhibit 5).

The portion of the legislative history cited by MANA demonstrates this concern. In its fuller context, the statement of Senator Graham selectively quoted in MANA's comments explains that Congress' goal "is to help keep important and safe chemicals available for minor-crop growers," given that "many pesticide companies have had to cancel their registrations for small volume crops." Senator Graham explains the purpose of the 1990 amendment as follows: "[t]he bill we are introducing today addresses specific problems in the registration process for minor-use growers. For example, we ask EPA to let affected grower groups know when a chemical they need is going to be removed from the market. That gives the growers the opportunity to take over the registration of the pesticide and continue to use it." 136 Cong. Rec. S5982 (May 10, 1990).[12]

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[11] Under FIFRA § 6(f)(3)(C), if a pesticide or use for which voluntary cancellation is sought includes a minor agricultural use, and if EPA determines that termination of that minor use would adversely affect the availability of the pesticide for use, then EPA must make reasonable efforts to inform persons who use the pesticide about the voluntary cancellation request and must provide a 180-day comment period. FIFRA provides a process whereby a registrant and a user may enter an agreement to transfer the registration to the user, instead of canceling the registration. *See* FIFRA § 6(f)(3)(A). Under certain circumstances, EPA "shall approve the transfer and shall not approve the request for voluntary cancellation or amendment to terminate use unless [EPA] determines that the continued use of the pesticide would cause an unreasonable adverse effect on the environment." FIFRA § 6(f)(3)(B).

[12] *See also* Statement of Senator Adams, 136 Cong. Rec. S5984 (May 10, 1990) (describing a "crisis" faced in the area of minor-use pesticides while explaining that "[i]f a chemical cannot meet our safety standards, it should not be used. What concerns me are situations where safe products become unavailable for our farmers, often without notice or the chance to develop alternatives. The intent of this bill, therefore, is to make sure those most immediately affected by reregistration -- America's minor crop farmers -- are given notice that chemical products they use may be affected by this process, and given an opportunity to see that the pesticide goes through the reregistration process. I believe this bill does this in ways consistent with FIFRA's overall public safety goals.").

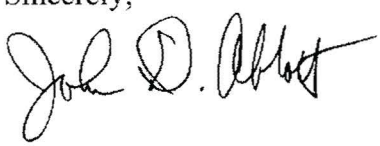
Consistent with the language and purpose of FIFRA § 6(f)(1)(C), EPA invited paraquat users to contact Syngenta if they wished to retain an old paraquat registration. *See* 70 Fed. Reg. 62112, 62117 (October 28, 2005). EPA's Federal Register Notice announcing an extension of the comment period for the voluntary cancellation maintains this statutory focus on users.[13] Since Syngenta's voluntary cancellation request was first announced in the Federal Register last year, no user has contacted Syngenta to request that the old paraquat registrations be maintained. In fact, as discussed above, numerous interested grower groups expressed their support of an EPA decision to cancel Syngenta's non-Inteon formulations. *See* EPA Docket No. EPA-HQ-OPP-2005-0285. Any potential concerns over minor use growers' access to pest control tools are eliminated by virtue of the fact that the Inteon formulation is registered and available for all the same uses as the old paraquat; Syngenta is offering access to the safer technology to paraquat registrants; and there are alternative pesticides available in the marketplace for the minor uses as well. There is no statutory basis to delay granting Syngenta's request for voluntary cancellation.

* * * * *

The new Sri Lanka human survey data, as well as the recent United States Inteon incident report, provide EPA with additional evidence of the type sought by BEAD in its assessment of the benefits to human health associated with use of the Inteon formulation. These new data also validate Syngenta's canine toxicokinetic studies and demonstrate the benefits of Inteon to human health will far outweigh the minimal costs to growers associated with the new formulation. The comments submitted by MANA and Griffin – which even on their merits fail to undercut EPA's conclusions in its Data Evaluation Records that Inteon is less toxic than earlier paraquat formulations – are wholly eclipsed by these new data. Their objections are also mooted by Syngenta's willingness to allow paraquat registrants access to the safer technology on commercially favorable terms. EPA should cancel Syngenta's sole remaining old paraquat registration, for which manufacture and Syngenta sales have ended, and deny the applications of any companies seeking to reintroduce riskier paraquat products in the United States.

Thank you for your consideration. If you have any questions regarding the data or would like any other information, please contact me directly at 336-632-7074 or john.abbott@syngenta.com.

Sincerely,



John D. Abbott, Ph.D.
Team Leader-Herbicides

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[13] MANA mischaracterizes the May 31, 2006 Federal Register notice in which EPA stated that a "*user seeking to apply for its own registration of that pesticide* may submit comments requesting EPA not to cancel a registration until its 'me-too' registration is granted." 71 Fed. Reg. 30919, 30919 (May 31, 2006) (emphasis added). EPA's Federal Register notice invites comments on the voluntary cancellation from users and does not commit EPA to grant me-too applications for the old paraquat formulation.

NAFTA Regulatory Affairs
Syngenta Crop Protection, Inc.

Attachments

cc: N. Zinn, EPA, Biological and Economic Analysis Division
J. Kim, EPA, Biological and Economic Analysis Division
A. Jones, EPA, Biological and Economic Analysis Division
I. Yusef , EPA, Biological and Economic Analysis Division
J. Jones, EPA, Office of Pesticide Programs
L. Rossi, EPA, Registration Division
D. Stubbs, EPA, Registration Division
J. Tompkins, EPA, Registration Division
H. Johnson, EPA, Registration Division

EXHIBIT 1

Improvement in survival following paraquat ingestion after introduction of a new formulation with INTEON® technology in Sri Lanka.

Wilks MF (1), Fernando R (2,10), Ariyananda PL (3), Eddleston M (4,10), Berry DJ (5), Tomenson JA (6), Buckley NA (7,10), Jayamanne S (8,10), Gunnell D (9), Dawson A(10). 1. Syngenta Crop Protection AG, Basel, Switzerland; 2. Department of Forensic Medicine and Toxicology, University of Colombo and National Poisons Information Centre, Sri Lanka; 3. Faculty of Medicine, University of Ruhuna, Sri Lanka; 4. Centre for Tropical Medicine, University of Oxford, UK; 5. Syngenta, Alderley Park, Macclesfield, UK; 6. Causation Limited, Macclesfield, UK; 7. Australian National University Medical School, Canberra, Australia; 8. Polonnaruwa Base Hospital, Sri Lanka; 9. Department of Social Medicine, University of Bristol, UK; 10. South Asian Clinical Toxicology Research Collaboration (SACTRC)

Objective: To compare the outcome of poisoning cases following the introduction of a new paraquat formulation, developed to have reduced oral toxicity, with the standard formulation of paraquat. **Methods**: Cases of paraquat poisoning presenting to nine base and general/teaching hospitals across Sri Lanka over a 26 month period were included. The survey protocol was approved by three Ethical Committees covering all hospitals and an independent Scientific Advisory Panel was established to oversee data collection and analysis. Informed consent was obtained from patients presenting following paraquat ingestion (or from their relatives), and a questionnaire was used to collect details of the circumstances of ingestion, treatment and outcome. Plasma and/or urine samples were obtained to identify which formulation had been ingested. Patients discharged from hospital were followed up after 3 months to ascertain survival. Starting in December 2003, data were collected over a 26 month period. During the first 10 months the only product containing paraquat available for sale in Sri Lanka was a standard 200g/l formulation. In October 2004, a novel 200g/l formulation with INTEON® technology (containing an alginate that converts to a gel under stomach acid conditions, increased levels of emetic, and a purgative) designed to reduce the amount of paraquat available for absorption was introduced. Problems were experienced with an apparent phase separation of the INTEON® formulation during the survey period, but it was decided to continue with the survey since it was felt that this was unlikely to influence the study's assessment of the safening potential of INTEON® technology. Survival analyses were performed using both non-parametric analyses (Kaplan-Meier and log rank trend tests) and semi-parametric methods (Cox's proportional hazards (PH) with adjustment for potential confounding factors). **Results:** Data from 586 patients were included in the analysis; 297 cases were recorded prior to October 2004 (standard formulation), and 289 cases had confirmed or probable INTEON® ingestion (195 confirmed by plasma or urine test). The average age of patients was 30 years and the majority were male (79%). Most (94%) were cases of deliberate ingestion. A higher proportion of patients having ingested INTEON® vomited within 15 min (55% vs. 38%), and fewer received gastric lavage (40% vs. 55%). The new formulation improved overall survival (p=0.005, log rank test) from 25.6% to 35.3% (difference 9.7%; 95% CI 2.3% - 17.1%). Survival was strongly associated with estimated ingestion volume, and the beneficial effect of INTEON® was apparent across the dose range. Cox PH regression analyses consistently showed a significant, approximately 2-fold reduction in toxicity (i.e. a shift in the dose response by a factor of 2) for INTEON® compared to standard product, suggesting a reduction of paraquat absorption. There was a small overall increase in median time to death from 0.9 days for standard product to 1.5 days for INTEON®, however, this effect was more apparent in those patients who had ingested lower doses (0-30ml) where median time to death increased from 2.8 days (IQR 0.7 – 8.7) to 5.0 days (IQR 2.0 – 9.5) thus raising the possibility of more time being available for treatments to be effective. **Conclusion:** The

survey has shown that INTEON® technology significantly improves the survival of patients following paraquat ingestion. Formulation developments have now overcome the phase separation problems and it is expected that this may lead to a further reduction in toxicity.

EXHIBIT 2

FERMIN BARRUETO JR MD
Assistant Professor

DEPARTMENT OF EMERGENCY MEDICINE

UNIVERSITY OF MARYLAND
SCHOOL OF MEDICINE

To Whom It May Concern:

I am reporting a case of a patient I treated who ingested Gramaxone INTEON® and had resulting severe pulmonary fibrosis. The case is summarized here.

A Severe Paraquat Ingestion that Survived

A 27 year old man, in a suicide attempt, ingested ½ a cup (4 ounces) of Gramoxone INTEON® (Syngenta), a 30% solution of paraquat, that was in his landscaping truck. Forty-five minutes after the ingestion, the patient vomited several times and went to the Emergency Department(ED). He complained of burning in his chest and mouth. He was admitted and had an esophagogastroduodenoscopy (EGD) performed which showed gastritis and superficial ulcerations of the esophagus, stomach and proximal duodenum. The patient was discharged after 24 hours of observation and returned to the ED 4 days later with hemoptysis and shortness of breath. He was immediately transferred to a tertiary care facility. He has no past medical or surgical history. He takes no prescription or herbal medications. Social history revealed he drinks alcohol 2-3 days a week and has used marijuana and cocaine in the past. Vital signs at the tertiary care facility were: temperature, 102.3°F; pulse, 108/minute; blood pressure, 132/71 mmHg; respiratory rate 31/minute; pulse oximetry, 90% on room air. This is a well nourished male in moderate respiratory distress. Head and neck exam revealed no oropharyngeal burns or ulcerations. Lung examination revealed diffuse rhonchi and tachypnea but no accessory muscle use. Cardiovascular examination revealed tachycardia but no murmur, rub or gallop. Abdominal examination was benign and neurologic examination revealed an alert and oriented man with no focal deficits.

Laboratory investigation included a comprehensive metabolic panel that revealed: Na+, 132 meq/L; K+, 3.0 meq/L; Cl-, 95 meq/L; CO2, 22 mmol/L; BUN, 57 mg/dL; Creatinine, 6.0 mg/dL; Ca2+, 9.2 mg/dL; Phosphorous, 3.5; Mg2+, 2.0 mg/dL; SGOT, 24 U/l; SGPT, 78 U/l; total bilirubin, 0.6 mg/dL. Complete blood cell count revealed WBC, 18.0 K/mcL; hemoglobin, 11.7 g/dL; hematocrit, 33.5; platelets, 162 K/mcL. A chest radiograph showed diffuse patchy infiltrates bilaterally, worse on the right than left. An arterial blood gas on room air revealed: pH, 7.47; PCO2 36 mmHg, PO2, 56 mmHg; HCO3, 25 mmol/L. A serum paraquat concentration performed by National Medical Services, Inc. four days after the ingestion was 0.08 mcg/mL (normal limit < 0.06 mcg/mL) by spectrophotometry (SP). A urine paraquat concentration also 4 days post-ingestion and by SP was 0.76 mcg/mL (asymptomatic sprayers up to 0.3 mcg/mL, urine).

Upon arrival to the tertiary care center, the patient was started on methylprednisolone, 1 g IV every day for 3 days and dexamethasone, 6 mg IV every 6 hours. He was also started on a cycle of cyclophosphamide, 1.7 g IV every day for 2 consecutive days. An infusion of acetylcysteine (Acetadote®) at a rate of 685 mg/hr was administered for 7 days as well as vitamin C and vitamin E supplementation

110 South Paca Street • 6th Floor, Suite 200 • Baltimore, Maryland 21201 • 410 328 8025 • 410 328 8026 *fax* • youremail@host.com

FERMIN BARRUETO JR MD
Assistant Professor

DEPARTMENT OF EMERGENCY MEDICINE

UNIVERSITY OF MARYLAND
SCHOOL OF MEDICINE

throughout the hospitalization. He required continuous veno-venous hemodialysis for 3 days followed by intermittent hemodialysis for 3 more days until his creatinine normalized to 1.4 mg/dL on HD #6 and did not require any further hemodialysis. The patient's respiratory status worsened requiring oxygen supplementation and at 2 L nasal cannula had a resting pulse oximetry of 80%. On hospital day #8, as he was moving himself to the lavatory, his pulse oximetry decreased to 70% which prompted a computed tomographic scan of the chest which revealed diffuse pulmonary fibrosis with a ground glass appearance and pneumomediastinum. An esophagram was performed and revealed no signs of perforation. Rapamycin therapy was initiated to limit any further pulmonary fibrosis on HD #12 and continued for 15 days. The patient became neutropenic with a WBC of 0.2 K/mcL prompting treatment with neupogen causing the WBC to peak at 29.6 K/mcL but returned to normal limits at 10.2 K/mcL. During his neutropenia secondary to the cyclophosphamide, the patient was covered empirically with piperacillin/tazobactam and vancomycin despite never mounting a fever or identifying a source of infection. On HD #14, the patient developed an iliofemoral deep venous thrombosis and had lovenox and coumadin therapy initiated. After HD #39, the patient's resting pulse oximetry was 90% on 2L NC, was able to perform basic activities of daily living and was stable for transfer to the inpatient psychiatric ward.

If there are any further questions about this case please feel free to contact me at 443 465 4289. Thank you.

Sincerely,

Fermin Barrueto Jr., MD
Assistant Professor
University of Maryland School of Medicine
Department of Emergency Medicine
Medical Toxicologist

110 South Paca Street • 6th Floor, Suite 200 • Baltimore, Maryland 21201 • 410 328 8025 • 410 328 8028 *fax* • youremail@host.com

EXHIBIT 3

From: Fermin Barrueto [mailto:fbarr001@umaryland.edu]
Sent: Dienstag, 18. Juli 2006 16:47
To: Wilks Martin CHBS
Subject: RE: Paraquat Report

Martin,

I hope everything has been going well for you. Our patient has been indeed discharged from the medical floor and was admitted to the inpatient psychiatric facility within the hospital. He has been there and will sat 90- 93% on 2LNC. Minimal improvement but he has at least made it off of the medical floor.

My opinion as far as the case for the report I gave you is that a combination of dose, Inteon technology and supportive care were all factors in the survival of this patient. Impossible to say for certain how important the role Inteon technology played, but if we believe the dose ingested - this was a several fold lethal dose and the patient survived. The delayed presentation to receive ICU care would lead me to believe that Inteon technology was a critical player in this patient's survival.

The paper is beginning to come together. I have finished my part and am awaiting everyone elses. I wish you the best and will talk to you later.

Fermin

EXHIBIT 4

Declaration of Sir Colin Berry

I, Sir Colin Berry, declare under penalty of perjury that the following is true and correct.

1. I am Professor Emeritus of Pathology at Queen Mary, London. . I am presently in active pathology practice and act as consultant in toxicology for regulatory agencies, pharmaceutical and agrochemical companies and for groups with environmental concerns. I serve on the advisory boards of "Sense about Science", the Scientific Alliance and am a consultant at the Science Media Center of the Royal Institution.
2. I was a member of the UK regulatory body for Pesticides for more than 20 years in various capacities; serving as Chairman of the Advisory Committee on Pesticides for 10 years – reporting to six government departments. I have also been Chairman of the Committee of Dental and Surgical Materials and served on the Committee of Safety of Medicines. In these capacities I have taken part in a number of reviews of many compounds, including UK, EU and WHO related reviews of Paraquat. My present publications relate mainly to risk evaluation and assessment and I have recently addressed the Parliamentary and Scientific Committee on related issues.
3. CV attached
4. I have been asked to provide my opinion as an expert in toxicology and pesticide testing on the reliability of Syngenta data for predicting human responses to ingestion of Syngenta's Inteon formulation.
5. This Declaration explains the biochemical mechanism of the Inteon formulation in the digestive tracks of mammals, the results of tests of Inteon when ingested by dogs, and the science supporting the application of these data to assessing the consequences of Inteon ingestion by humans.

Biochemical Mechanism of Inteon

6. The main site of absorption of paraquat is the small intestine, particularly the jejunum (the central section of the small intestine), with limited absorption from either the oesophagus or stomach (Heylings, 1991). The oral toxicity of paraquat may therefore be reduced by limiting the exposure of the small intestine to ingested paraquat material.
7. The key to Inteon's safety mechanism is the formation of an alginate gel in the stomach that helps prevent the release of any paraquat into the small intestine. Alginates are non-toxic carbohydrates of polymannuronic and polyguluronic acid and are commonly used in the food industry as gelling agents. They are also used therapeutically, for example in treating dyspepsia (Mandel *et al*, 2000) and wound healing (Agren, 1996). An alginate that gels under low pH conditions (pH 1-3) was selected for Inteon, as the material remains liquid and flowable as a formulation, but if it is swallowed and reaches the acidic conditions of the stomach, it forms a semi-solid gel. This change holds the material in the stomach, and allows emesis (vomiting) to be more effective in removing the semi-solid material than it would be in removing a liquid. Inteon also contains an emetic agent that induces vomiting following ingestion.

8. The gelling process reduces the amount of paraquat that might be released to the small intestine.

Results of Toxicity Study on Inteon Formulation in Dogs

9. Inteon formulations have been shown to reduce the systemic absorption of paraquat in the dog, resulting in a greater than ten-fold reduction in oral toxicity when compared with non-Inteon paraquat formulations (Brammer et al. 2004).

Extrapolation from dogs to humans

10. The choice of the dog in Syngenta's experiments depends on this species having the necessary digestive attributes, including a vomit reflex. The vomit reflex is controlled centrally by the vomit centre in the brain, responding to changes in cAMP (a molecule that regulates several biological processes) -- which is the same in dog and man. This is significant because phosphodiesterase inhibitors, like Syngenta's emetic agent (PP796), work through a cAMP-regulated process. It is worth noting that other species such as the rat were deemed inappropriate since rats do not vomit.
11. The toxicokinetics processes for paraquat (and many drugs and other chemicals) are similar in dog and humans. Dogs, like humans are omnivores and intermittent feeders. The physiology of digestion in both species is also very similar.

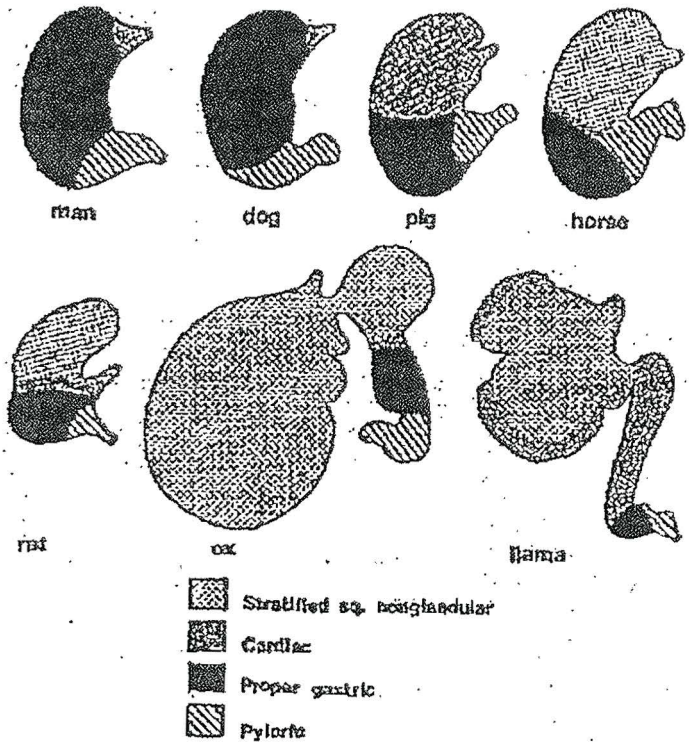
Reactions to paraquat in dog and human

12. Data in man indicate that the plasma paraquat kinetic profile and area under the curve (AUC) at a minimally toxic dose is similar between dog and man. Across species there are differences in the acute oral lethal dose which is thought to be due to differences in the amount of paraquat absorbed from the gastrointestinal tract. Analysis of the 0-24h AUC across these species shows similar paraquat systemic exposure at a peri-lethal oral dose (Heylings, 1994).

Comparable gastrointestinal tract characteristics

13. It was concluded by Kararli (1995) that current data indicated that no single animal can mimic the gastrointestinal tract characteristics in humans. However, in considering stomach morphology and emptying characteristics, the dog and human were found to be very similar. The Inteon technology is predominantly focused on the interactions within the stomach in order to prevent the ingested dose from reaching the intestine. The stomach size, volume and pH are similar between dog and man.

Figure 1. Variations in the type and distribution of gastric lining tissue in different mammals. The dog and human are closest in structure of stomach tissue. (Stomachs are not drawn to scale).



Humans have a highly regulated gastrointestinal physiology. The human digestive system is sensitive to a variety of potentially ingested toxins and is particularly sensitive to topical irritants of the gastric mucosa (lining tissue), some bacterial and viral toxins, and foods and drinks that have a high salinity. Vomiting can be initiated centrally or locally.

14. Local irritation by compounds (such as alcohol or paraquat) is a slow and inefficient emetic stimulus, while centrally acting emesis (mediated via the hypothalamus) is very efficient in all higher mammals. The vomit centre, once triggered, causes a complete closure of the pyloric sphincter, followed by gastric muscle contraction from the pylorus upwards through the fundus. Following relaxation of the oesophageal sphincter, the pressure effect expels the gastric contents very effectively. There is no anatomical or physiological reason why human vomiting should be less effective than that seen in dogs.

Emesis in dogs and humans

15. The efficiency of emesis (vomiting) generally depends on the dose of the emetic and the physical constitution of the stomach contents. When ingested, the Inteon product gels and stays in the stomach while the human receives a dose of the emetic (PP796) that causes prompt emesis, coupled with closure of the pylorus. Human vomiting will be as productive as vomiting by the dog. From analysis of poisoning data reported by Meredith and Vale (1987), the threshold dose of the PP796 emetic required to produce emesis in 100 percent of human patients within 30 minutes was greater than or equal to 0.2mg/kg. It is important to note that this is also the threshold dose in the administration of Inteon formulations in the dog (Brammer et al 2004).

Conclusion

16. The similarities between the human and dog gastrointestinal systems, including similar stomach emptying and emesis processes, allow for valid extrapolation from dog toxicokinetics studies to reach a determination of human responses to ingestion of Inteon formulation.

References

1. Heylings JR (1991). Gastrointestinal absorption of paraquat across the isolated mucosa of the rat. *Toxicol. Appl. Pharmacol.* 107, 482-493.

2. Mandel KG, Daggy BP, Brodie DA, Jacoby HI (2000). Alginate-raft formulations in the treatment of heartburn and acid reflux. *Ailment Pharmacol Ther.* 14(6):669-90

3. Agren MS (1996). Four alginate dressings in the treatment of partial thickness wounds: A comparative experimental study. *J. Plast. Surg.* 49:129-1:34.

4. Schiller LR (1999). Clinical pharmacology and use of laxatives and lavage solutions. *J. Clin. Gastroenterol.* 28(1):1 1-8

5. Brammer A, Heylings JR and Swain C (2004). Paraquat 240 g/l SL formulation (A7813K): Toxicokinetic study in the dog. Syngenta Report No: CTL/XD7355/REGULATORY/REPORT. (MRID 46364510, Submission Date: Sept. 16, 2004.)

6. Meredith and Vale, JA (1995). Treatment of paraquat poisoning: gastrointestinal decontamination. In *Paraquat Poisoning: Mechanisms, Prevention, Treatment*, Ed Bismuth, C. and Hall, A.H., Marcel Dekker, New York, pp. 297-314.

7. Kararli (1995). Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. *Biopharmaceutics & Drug Disposition* 16 351-380.

8. Heylings (1994) Paraquat: Acute Oral Toxicity - A species comparison. Syngenta Report No CTL/R/1175.

January 16th, 2006

Sir Colin Berry

CURRICULUM VITAE

PROFESSOR SIR COLIN BERRY

Date of Birth	28th September, 1937
Nationality	British
Status	Married, 2 children

QUALIFICATIONS

MB BS	(London)	May 1961
MD	(London)	Sept 1968
PhD	(London)	May 1970
DSc	(London)	Nov 1992
Hon MD Ionnina (Greece)		Sept 2003
MRCPath		Nov 1967
FRCPath		April 1979
FFPM		August 1989
FRCP		July 1993
FFOM		May 1995
FRCP (Ed)		June 1998
FAcad Med Sci		

PREVIOUS APPOINTMENTS

House Physician	Charing Cross Hospital	July '61-Jan. '62
House Surgeon	Charing Cross Hospital	Jan. '62-July '62
Senior House Officer in Pathology	Charing Cross Hospital	July '62-July '63
Registrar in Pathology	Charing Cross Hospital	July '63-July '64
Senior Registrar in Pathology	Fulham Hospital	July '64-Oct. '64
Lecturer & Senior Lecturer in Morbid Anatomy	Hospital for Sick Children & Institute of Child Health, London	Nov. '64-Dec. '68
British Heart Foundation Senior Res. Fellow & Hon Lecturer in Pathology	Institute of Child Health, London	Jan. '68-Oct. '70
University Reader in Pathology & Hon Consultant Pathologist	Department of Histopathology, Guy's Hospital Medical School	Oct. '70-Sept '76
Deputy Director	IRC Biomedical Materials, Queen Mary & Westfield College, London	
Visiting Professor	University of Singapore	Oct. '88-Jan. '89

MAJOR aPPOINTMENTS

Professor of Morbid Anatomy Director of the Pathological Institute, Consultant Histopathologist	The Royal London Hospital	Oct. '76
Dean-Elect and Dean	The London Hospital Medical College	Dec. '92-July '94
Warden	St Bartholomew's & The Royal London School of Medicine & Dentistry	July '94-Sept '96

DISTINCTIONS

Civil

Knight Bachelor, Birthday Honours List	June	1993

Undergraduate

Govemors Clinical Gold Medal
Llewllyn Scholarship
Gordon M Holmes Prize in Medicine
Norman C Lake Prize in Surgery
Pierer Prize in Clinical Subjects
Steadman Prize in Pathology
Year Prizes in Orthopaedics
Otorhinolaryngology
Ophthalmology
Psychological Medicine
Dermatology
Huxley Prize in Physiology

Postgraduate

Gillson Scholarship in Pathology - Worshipful Society of Apothecaries of London	1967 - 1968	
Re-awarded	1970 - 1972	
Founder Member by Distinction of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of London	1989	
Corresponding Member, Rheinish-Westfalische Akademie der Wissenschaften	May	1993
Member, Deutsch Akademie der Naturforscher „Leopoldina"	Oct.	1993
Honorary Fellow Faculty of Occupational Medicine of the Royal College of Physicians	May	1995
Honorary Fellow of the University of Central Lancashire		1999
Corresponding Member, The German Pathological Society	May	2002
Honorary Fellow, The German Pathological Society	May	2005

RELEVANT ADMINISTRATIVE POSTS AND APPOINTMENTS HELD

The London Hospital Medical College

Professor of Morbid Anatomy and Director of the Institute of Pathology	1976 -
Chairman of Academic Board, Academic Session	1989 - 1990
Member of the Clinical Curriculum Group	
Member of the City and East London Confederation Joint Academic Committee	1988 -
Dean-Elect The London Hospital Medical College	1992 - 1994
Dean, The London Hospital Medical College	1994 - 1994
Warden and Vice Principal of Medicine and Dentistry, Queen Mary and Westfield College	1994 - 1996

President

European Society of Pathology	1989 - 1991
(President-Elect)	1987 - 1989
Developmental Pathology Society	1976 - 1980
British Academy of Forensic Sciences	2003 - 2005
(President Elect)	2001 - 2003

Chairman

Advisory Committee on Pesticides, Ministry of Agriculture, Fisheries and Food	1988 - 1999
(Member)	1981 - 1988
Scientific Sub-Committee on Pesticides of the Ministry of Agriculture, Fisheries and Food and Department of Education and Science	1985 - 1988
(Member)	1977 - 1985
Committee of Dental and Surgical Materials	1982 - 1992
(Member)	1978 - 1981
Physiological Systems and Disorders Board of the Medical Research Council	1990 - 1992
(Member)	1988 - 1990
National Health & Medical Research Council Independent Panel of Assessors, Commonwealth of Australia	1982 - 2000
Association of Professor of Pathology	1987 - 1989
Union Europeenne des Medecins Specialistes, Board of Anatomic Pathology	1990 - 2001
Council, Research Defence Society	1993 - 1996

Master

The Worshipful Society of Apothecaries of the City of London (Senior Warden 2001 -2002, Junior Warden, 2000-2001) Treasurer 2004-	2003 – 2004

Secretary

Foundation Secretary, Developmental Pathology Society	1971 - 1975
Meetings Secretary, Association of Clinical Pathologists	1980 - 1982
Hon Secretary, Association of Clinical Pathologists	1982 - 1985
Secretary, Federation of Associations of Clinical Professors	1987 - 1990

Member

Medical Research Council	1990 - 1994
Toxicology Group, Expanded Programme on Human Reproduction, World Health Organization	1979 - 1985, 1987 - 1989, 1992 -
Committee of Toxicity of Chemicals in Food, Consumer Products and the Environment	1984 - 1989
Committee on Safety of Medicines	1990 - 1992
Committee on Safety of Medicines Advisory Panel	1994- 2002
Scientific Committee for Pesticides of the Commission of the European Communities	1985 - 1989
General Dental Council's Panel of Visitors of Examinations	1985 - 1987
Research Defence Society Council	1992 - 1998
N.E. Thames Regional Research and Development Committee	1992 - 1994
Ministry of Agriculture, Fisheries and Food Pesticide Safety Directorate Ownership Board	1993 - 1999
General Medical Council	1993 - 1996
Council of the British Toxicology Society	1994 - 1996
General Dental Council	1994 - 1996
Steering Committee on Environment and Health European Science Foundation	1996 - 2000
Member of the Gulf War Investigation Illness Research Programme Steering Committee.	1996 - 2000
Member of the Evaluation Board, National Institute for Clinical Excellence	1999 - 2002
Member of the Board of Science and Policy Advisors, The American Council on Science and Health	2002 -
Programme Committee, European Science Open Forum 2004	2000 - 2004
Steering Committee, European Science Open Forum 2006.	2004 -
Advisory Board, The Scientific Alliance	2003 -
Advisory Council, Sense About Science	2003 -

Royal College of Pathologists

Assistant Registrar	1981 - 1984
Treasurer	1988 - 1993

Scientific Advisor

Ministry of Agriculture Scientific Advisor to the British Industrial Biological Research Association	1986 - 1989

Chief Medical Officer's Committees

Standing Medical Advisory Committee	1988 - 1992
Academic Forum	1988 - 1991

Charitable

Advisor, The Infantile Hypercalcaemia Foundation Medical Advisory Panel	1980 -

Chairman of Trustees of Advance in Medicine (AIM), a medical charity of The Royal London Hospital	1984 -
Appeals Committee, Royal College of Pathologists	1989 – 1993
Appeals Committee, Royal College of Pathologists	2005 -
And several other medical charities	

EXAMINATION APPOINTMENTS

External Examiner for BSc examinations in London Colleges (Anatomy and Pathology) and in Manchester University, The University of Glasgow and of Wales
Final BDS (Pathology) for the Schools of Dentistry of the Universities of London, Cardiff, Edinburgh and Leeds
Senior Examiner for the Final MB BS (Pathology) University of London
External Examiner for the Final MB BS (Pathology), Universities of Cambridge, Wales Belfast and Oxford
Visiting Examiner in Pathology of the University of Benin, Nigeria, the National University of Singapore, and Chinese University, Hong Kong
External Examiner in Applied Toxicology, University of Surrey

I have also acted as Examiner for more than 40 PhD or MD theses in the Universities of London, Manchester, Cambridge, Guilford, Dublin, Leicester and Liverpool and for the University of Christchurch, New Zealand

Member of the Panel of Examiners for the Final MRCPath (Histopathology)

External Examiner DSc, Liverpool
Local Examiner for (i) Part I BDS and
(ii) MB BS Pathology
Member of the MD Panel, University of London

OTHER PROFESSIONAL ACTIVITIES

I was Joint Managing Editor of the Journal "Virchows Archiv" for 25 years.

I am a member of the Editorial Boards of:
- Archives of Toxicology
- British Journal of Experimental Pathology
- Human Toxicology
- Journal of Pathology
- Patologica

I am a referee for:
- Annals of Contemporary Diagnostic Pathology
- Archives of Diseases in Childhood
- British Heart Journal
- British Journal of Surgery
- British Medical Journal
- Carcinogenesis
- Journal of Cardiovascular Research
- Journal of Clinical Pathology
- Journal of Hypertension
- Journal of Medical Genetics
- Journal of Pathology
- Lancet
- Nature
- Paediatric Research

and have reviewed books for these and other journals

MAJOR INVITED LECTURES

Arris and Gale Lecturer, Royal College of Surgeons of England		1973
Sir Frederick Bawden Lecturer, British Crop Protection Council		1990
John Hull Grundy Lecturer, Royal Army Medical College		1992
Distinguished Visitor Lecture, College of Pathologists of Australia, Cairns	Sept	1993
Lucas Industries Lecturer, Royal College of Physicians	May	1994
Gesselschaft Deutscher Chemiker Lecturer, Bayer AG Leverkusen, Germany	Nov	1994
The Royal Institution of Great Britain; Friday Evening Discourse	Feb	1995
Plenary Lecture 6th International Congress of Toxicology, Seattle	July	1995
First Anniversay Lecture, University of Central Lancashire	July	1996
5th Robert Lane Lecturer, University of Manchester	Nov	1996
Apothecaries' Lecture, Society of Occupational Medicine	Feb	1997
'ASCEPT' Toxicology Lecture	Sept	1997
Sentry Farming Conference 'Farming '98', Cambridge	Feb	1998
Plenary Lecturer 9th International Congress of Pesticide Chemistry, London	Aug	1998
National Farmers Union Annual Address	Feb	1999
University of Ontario (Guelph) 125th Anniversary Lecture	March	1999
The Institute of Biology Northern Branch Charter Lecture, University of Newcastle upon Tyne	Oct	2000
The Royal Institution of Great Britain; Friday Evening Discourse	March	2001
International Life Science Institute; Plenary lecture. Miami	Jan	2002
Scientific Alliance; Risk and GM Crops meeting.	March	2002
Public Debate with the Secretary of State for Agriculture Bloomberg Auditorium. London	Jan	2004
Society of the Chemical Industry; Plenary lecture. Edinburgh	March	2004
The Precautionary Principle, ESOF 2004	August	2004

The Sir Michael Davies Lecture, The Expert Witness Institute	April	2005
Presidential Address, BAFS	June	2005

EXHIBIT 5

EXECUTIVE REPORTS OF COMMITTEES

The following executive reports of committees were submitted:

By Mr. WARNER, from the Committee on Armed Services:

The following-named officer for appointment to the grade of rear admiral in accordance with article II, section 2, clause 2, of the Constitution:

To be rear admiral

Capt. Robert C.J. Krasner, MC, U.S. Navy, 155-36-6716.

By Mr. BIDEN, from the Committee on the Judiciary.

Stanley F. Birch, Jr., of Georgia, to be U.S. circuit judge for the Eleventh Circuit;

John D. Rainey, of Texas, to be U.S. district judge for the Southern District of Texas;

James K. Singleton, Jr., of Alaska, to be U.S. district judge for the District of Alaska;

William M. Nickerson, of Maryland, to be U.S. district judge for the district of Maryland;

Stephen M. McNamee, of Arizona, to be U.S. district judge for the District of Arizona;

Jack D. Shanstrom, of Montana, to be U.S. District Judge for the District of Montana;

Samual Grayson Wilson, of Virginia, to be U.S. district judge for the Western District of Virginia;

Richard W. Vollmer, Jr., of Alabama, to be U.S. district judge for the Southern District of Alabama;

Arthur F. Van Court, of California, to be U.S. Marshal for the Eastern District of California for the term of 4 years; and

Daniel J. Horgan, of Florida, to be U.S. Marshal for the Southern District of Florida for the term of 4 years.

By Mr. BIDEN, from the Committee on the Judiciary:

Morris Lee Thompson, of Kansas, to be U.S. attorney for the District of Kansas for the term of 4 years.

(The above nomination was reported with the recommendation that it be confirmed, subject to the nominee's commitment to respond to requests to appear and testify before any duly constituted committee of the Senate.)

INTRODUCTION OF BILLS AND JOINT RESOLUTIONS

The following bills and joint resolutions were introduced, read the first and second time by unanimous consent, and referred as indicated:

By Mr. GRAHAM (for himself, Mr. ADAMS, and Mr. INOUYE):

S. 2604. A bill to facilitate the use of pesticides that are registered for agricultural minor uses, to establish the Inter-Regional Research Project Number 4 (IR-4 Program), and for other purposes; to the Committee on Agriculture, Nutrition, and Forestry.

By Mr. PRYOR (for himself, Mr. ADAMS, Mr. BUMPERS, Mr. BURDICK, Mr. CONRAD, Mr. EXON, Mr. KERREY, and Mr. KOHL):

S. 2605. A bill to amend title XIX of the Social Security Act to provide mechanisms to control Medicaid drug prices while assuring that beneficiaries receive quality medical care, physicians' prerogative to prescribe is protected and the role of pharmacists is enhanced; to the Committee on Finance.

By Mr. BURNS (for himself and Mr. BAUCUS):

S. 2606. A bill for the relief of Conwell F. Robinson and Gerald R. Robinson; to the Committee on Energy and Natural Resources.

By Mr. CRANSTON (for himself, Mr. MURKOWSKI, Mr. KERRY, and Mr. SANFORD):

S. 2607. A bill to amend the International Claims Settlement Act of 1949 to provide for the payment of claims of nationals of the United States against Vietnam; to the Committee on Foreign Relations.

By Mr. GLENN (for himself, Mr. LIEBERMAN, Mr. KOHL, Mr. PRYOR, Mr. METZENBAUM, Mr. LEVIN, Mr. SASSER, Mr. COHEN, Mr. NUNN, Mr. BINGAMAN, Mr. BUMPERS, Mr. HARKIN, and Mr. KENNEDY):

S. 2608. A bill to amend the Inspector General Act of 1978 to clarify the authority of Inspectors General to conduct audits and investigations; to the Committee on Governmental Affairs.

By Ms. MIKULSKI:

S. 2609. A bill to establish a national advanced technician training program, utilizing the resources of the Nation's 2-year associate-degree-granting colleges to expand the pool of skilled technicians in strategic advanced technology fields, to increase the productivity of the Nation's industries, and to improve the competitiveness of the United States in international trade, and for other purposes; to the Committee on Labor and Human Resources.

By Mrs. KASSEBAUM:

S. 2610. A bill to protect the free flow of commerce on the Missouri River; to the Committee on Environment and Public Works.

SUBMISSION OF CONCURRENT AND SENATE RESOLUTIONS

The following concurrent resolutions and Senate resolutions were read, and referred (or acted upon), as indicated:

By Mr. KENNEDY:

S. Res. 282. Resolution expressing the sense of the Senate regarding United States military assistance for the Republic of Liberia and human rights abuses in Liberia; to the Committee on Foreign Relations.

By Mr. SASSER from the Committee on the Budget:

S. Con. Res. 129. Original concurrent resolution setting forth the congressional budget for the U.S. Government for fiscal years 1991, 1992, 1993, 1994, and 1995; placed on the calender.

STATEMENTS ON INTRODUCED BILLS AND JOINT RESOLUTIONS

By Mr. GRAHAM (for himself, Mr. ADAMS, and Mr. INOUYE):

S. 2604. A bill to facilitate the use of pesticides that are registered for agricultural minor uses, to establish the Inter-regional Research Project Number 4 (IR-4 Program), and for other purposes; to the Committee on Agriculture, Nutrition, and Forestry.

MINOR USE PESTICIDES ACT

Mr. GRAHAM. Mr. President, today I am introducing, on behalf of myself, Senator INOUYE, and Senator ADAMS, a bill to amend Federal pesticide law. Our bill will ease the bureaucratic and economic restrictions that hamper the development and use of safe pesticides for fruits, vegetables, and specialty crops.

Our aim is to help keep important and safe chemicals available for minor-crop growers, and at the same time, encourage USDA to develop alternative pest control measures through integrated pest management and research. In many ways, we are creating an orphan-drug program for agricultural chemicals.

Because of the costs of reregistering an existing chemical with EPA, or because of the costs of developing a new chemical, many pesticide companies have had to cancel their registrations for small volume crops.

In other words, when weighing the costs of reregistering a pesticide for use on celery, the manufacturer must decide whether the volume of sales justifies the expense of the required tests and fees. In many cases, the decision will be against pursuing the registration for crops, like celery, that are not widely grown.

The impact on minor crop producers—who grow crops that range from apples to zucchinis—has been a shrinking pool of solutions to their pest problems. The end result will be at the grocer's produce counter—costlier, and perhaps fewer, fruits, vegetables.

The bill we are introducing today addresses specific problems in the registration process for minor-use growers. For example, we ask EPA to let affected grower groups know when a chemical they need is going to be removed from the market. That gives the growers the opportunity to take over the registration of the pesticide and continue to use it.

While we are concerned about the needs of the growers, our bill does not affect EPA's ability to remove suspect or dangerous chemicals from use. Our goal is to keep viable and safe pesticides from being discontinued purely for economic reasons—not to keep hazardous pesticides on the market.

Minor-use crops are grown in almost every one of our States. New Jersey blueberries, Massachusetts cranberries, Washington apples, Florida oranges, California avocados, all considered minor-use, and all more popular than ever with the health conscious American consumer.

But because of their nonprogram status, few of our research and development efforts are geared toward these specialty crop needs. Therefore, we are asking USDA to conduct more research on the pest control needs of minor crops, and to increase their emphasis on integrated pest management for minor crops.

Our bill also increases the authorization for the Inter-Regional, or IR-4, program. The most valuable research program for minor crops, the IR-4 program tests the safety of commercially nonviable minor-use pesticides. Underfunded and over burdened with work, the IR-4 program needs a boost in support from Congress.

The men and women who produce America's fruits, vegetables, and spe-

cialty crops are independent, hard-working, and proud of the way they make their living. We want, through our bill, to give them the tools they need to improve their farming practices, and to ensure that Americans will have access to an abundance of safe, delicious produce.

Before closing, I want to make special note of the work that Senator Matsunaga and his staff put into this bill. Senator Matsunaga was keenly aware of the problems his home-State producers faced and worked diligently to craft the legislation before us.

Mr. President, I ask unanimous consent that the text of the bill appear immediately following my remarks.

There being no objection, the bill was ordered to be printed in the RECORD, as follows:

S. 2604

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Minor Use Pesticides Act of 1990".

(b) TABLE OF CONTENTS.—The table of contents is as follows:

TITLE I—REGISTRATION OF PESTICIDES FOR AGRICULTURAL MINOR USES

SEC. 101. DATA IN SUPPORT OF REGISTRATION.

Section 3(c)(2)(A) of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136a(c)(2)(A)) is amended by inserting after the third sentence the following new sentence: "The Administrator shall not require a person to submit, under this Act, any data related to residues of a pesticide registered for a minor agricultural use in a geographic area where the use of the pesticide is not likely, as determined by the Administrator.".

SEC. 102. WAIVERS OF LIABILITY FOR PESTICIDES REGISTERED FOR MINOR AGRICULTURAL USES.

Section 3(f) of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136a(f)) is amended by adding at the end the following new paragraph:

"(4) WAIVERS OF LIABILITY FOR PESTICIDE REGISTERED FOR MINOR AGRICULTURAL USES.—In the case of a pesticide that is registered for a minor agricultural use, an agricultural producer may enter into a written agreement with the registrant of the pesticide to waive any liability of the registrant to the producer incurred with respect to the use.".

SEC. 103. REDUCTION OR WAIVER OF FEES FOR PESTICIDES REGISTERED FOR MINOR AGRICULTURAL USES.

Section 4(i)(4) of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136a-1(i)(4)) is amended by adding at the end the following new subparagraph:

"(D) Notwithstanding any other provision of this Act, in the case of a pesticide that is registered for a minor agricultural use, the Administrator may reduce or waive the payment of a fee for the registration or registration of the pesticide for the use if the Administrator determines that the fee would significantly reduce the availability of the pesticide for the use.".

SEC. 104. VOLUNTARY CANCELLATION.

Section 6(f) of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136d(f)) is amended—

(1) by striking paragraph (1) and inserting the following new paragraph:

"(1) VOLUNTARY CANCELLATION.—

"(A) A registrant may, at any time, request that a pesticide registration of the registrant be canceled or amended to terminate one or more pesticide uses.

"(B) Before acting on the request, the Administrator shall publish in the Federal Register a notice of the receipt of the request.

"(C) In the case of a pesticide that is registered for a minor agricultural use, if the Administrator determines that the cancellation or amendment of the registration of the pesticide for the use would adversely affect the availability of the pesticide for the use, the Administrator—

"(i) shall publish in the Federal Register a notice of the receipt of the request and take such other actions as are necessary to inform persons who so use the pesticide of the request; and

"(ii) may not approve or reject the request until the termination of the 90-day period beginning on the date of publication of the notice in the Federal Register, and

"(iii) the Administrator may waive the 90-day period if the Administrator determines that the continued use of the pesticide would pose an unreasonable adverse effect on the environment.

"(D) Subject to paragraph (3)(B), after complying with this paragraph, the Administrator may approve or deny the request."; and

(2) by adding at the end the following new paragraph:

"(3) TRANSFER OF REGISTRATION OF PESTICIDES REGISTERED FOR MINOR AGRICULTURAL USES.—In the case of a pesticide that is registered for a minor agricultural use:

"(A) During the 90-day period referred to in paragraph (1)(C)(ii), the registrant of the pesticide may notify the Administrator of an agreement between the registrant and persons who so use the pesticide (or an agreement between the registrant and a third party registrant, as defined by the Administrator) to transfer the registration of the pesticide, in lieu of canceling or amending the registration to terminate the use.

"(B) The Administrator shall approve the transfer of the registration of the pesticide unless the Administrator determines that the continued use of the pesticide would pose an unreasonable adverse effect on the environment.

"(C) If the Administrator approves the transfer and the registrant transfers the registration of the pesticide, the Administrator shall not cancel or amend the registration, or rescind the transfer of the registration, during the 180-day period beginning on the date of the approval of the transfer.

"(D) The new registrant of the pesticide shall assume the outstanding data and other requirements for the pesticide that are pending at the time of the transfer.".

SEC. 105. PEST CONTROL.

Section 28 of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136w-3) is amended to read as follows:

"SEC. 28. PEST CONTROL.

"(a) IN GENERAL.—

"(1) PESTS.—The Administrator, in cooperation with the Secretary of Agriculture, shall identify—

"(A) pests affecting minor-use crops that must be brought under control; and

"(B) chemical control measures available to control the pests described in subparagraph (A) and biological and other alternative control measures available to control the pests.

"(2) REPORT BY SECRETARY.—The Secretary of Agriculture shall, not later than 180 days after the date of enactment of this section and annually thereafter, prepare a report and send the report to the Administrator. The report shall—

"(A) describe in detail the pests and measures of pest control described in subparagraphs (A) and (B) of paragraph (1);

"(B) identify areas of pest control at risk of losing effectiveness due to—

"(i) an insufficient number of registered pesticides; or

"(ii) resistance by a pest to pest control measures; and

"(C) describe in detail research efforts, including agricultural extension programs, to develop effective pest control to address the areas of pest control described in subparagraph (B).

"(b) INTEGRATED PEST MANAGEMENT.—The Administrator, in cooperation with the Secretary of Agriculture, shall develop approaches to the control of pests based on integrated pest management that respond to the needs of producers who use pesticides for minor agricultural uses.".

SEC. 106. CONFORMING AMENDMENTS TO TABLE OF CONTENTS.

The table of contents in section 1(b) of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. prec. 121) is amended—

(1) by adding at the end of the items relating to section 3(f) the following new item:

"(4) Waivers of liability for pesticide registered for minor agricultural uses.";

(2) by adding at the end of the items relating to section 6(f) the following new item:

"(3) Transfer of registration of pesticides registered for minor agricultural uses.";

and

(3) by striking the items relating to section 28 and inserting the following new items:

"Sec. 28. Pest control.
"(a) In general.
"(1) In general.
"(2) Report by Secretary.
"(b) Integrated pest management.".

TITLE II—INTER-REGIONAL RESEARCH PROJECT NUMBER 4 (IR-4 PROGRAM)

SEC. 201. FINDINGS.

Congress finds that—

(1) the Inter-Regional Research Project Number 4 (IR-4 program) is a national research program intended to facilitate the registration of pesticides for minor agricultural uses where use volume does not justify commercial development;

(2) the main beneficiaries of the IR-4 project are agricultural producers who use the pesticides to produce crops that are eaten daily (such as vegetables, fruits, and

nuts) and crops that that enrich the environment (such as ornamental plants, floral crops, trees, and turfgrass);

(3) as the result of insufficient funding, the IR-4 program has a backlog of 1,200 requests for new uses;

(4) section 4 of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136a-1) requires the reregistration of over 4,000 currently labeled uses;

(5) about 1,000 priority minor use needs will not be supported for reregistration by industry;

(6) the IR-4 program is in a funding crisis; and

(7) without additional funds to meet the needs generated by reregistration requirements imposed by section 4 of such Act, and new environmental management methods, the IR-4 program will be unable to fulfill its important tasks.

SEC. 202. INTER-REGIONAL RESEARCH PROJECT NUMBER 4 (IR-4 PROGRAM).

Section 2 of the Act entitled "An Act to facilitate the work of the Department of Agriculture, and for other purposes", approved August 4, 1965 (7 U.S.C. 450i), is amended—

(1) by redesignating subsections (e) through (i) as subsections (f) through (j), respectively;

(2) by inserting after subsection (d) the following new subsection:

"(d)(1) The Secretary of Agriculture shall establish an Inter-Regional Research Project Number 4 (hereinafter referred to in this section as the 'IR-4 Program') to assist in the collection of residue and efficacy data in support of—

"(A) the registration or reregistration of minor use pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 et seq.); and

"(B) tolerances for residues of minor use chemicals in or on raw agricultural commodities under section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a).

"(2) The Secretary shall carry out the IR-4 program in cooperation with the Administrator of the Environmental Protection Agency, State agricultural experiment stations, colleges and universities, extension services, private industry, and other interested parties.

"(3) As part of carrying out the IR-4 program, the Secretary shall—

"(A) develop analytical techniques applicable to residues of pesticides registered for minor agricultural use, including automation techniques and validation of analytical methods; and

"(B) participate in research activities aimed at reducing residues of pesticides registered for minor agricultural use.

"(4) There are authorized to be appropriated $25,000,000 for fiscal year 1991, and such sums are necessary for subsequent fiscal years, to carry out this section."; and

(3) in subsection (h) (as redesignated by paragraph (1) of this section), by striking "subsection (b)" and inserting "subsections (b) and (d)".

SEC. 203. CONFORMING AMENDMENTS.

(a) Section 1449 of the National Agricultural Research, Extension, and Teaching Policy Act of 1977 (7 U.S.C. 3241) is amended by striking "sections 2(e), 2(f), and 2(h)" and inserting "sections 2(f), 2(g), and 2(i)".

(b) Section 1469(1) of such Act (7 U.S.C. 3315(1)) is amended by striking "sections 2(e), 2(f), and 2(h)" and inserting "sections 2(f), 2(g), and 2(i)".

Mr. INOUYE. Mr. President, I rise today in support of this important legislation designed to manage the use of pesticides on minor agricultural crops. I am pleased to join my colleagues, Senators GRAHAM and ADAMS, as an original sponsor of this initiative.

Mr. President, the Federal Government registers chemical pesticides and regulates their use on major crops such as cotton, wheat, corn, and soybeans. There is a sufficient demand for these pesticides. However, when it is a minor agricultural crop, pesticide regulations are more problematic. Due to the costly and lengthy registration process, I believe that special attention must be devoted to the development and registration of safe and effective chemical pesticides for these crops.

All of Hawaii's agricultural industries are considered minor crops. Even sugar—our largest crop in terms of acreage and value—is considered a minor crop. In an effort to diversify our agricultural base, Hawaii's farmers have taken bold steps and experimented with new crops. Coffee, cocoa, and vanilla crops have been planted in Hawaii. These ventures hold great promise for Hawaii's agricultural community for, if successful, will be the only crops of its kind in the Nation. Additionally, we are proud of our ongoing pineapple, papaya, macadamia nut, guava, and array of tropical flower industries. All of these crops, and numerous others, are considered minor. Many of these industries are involved in pesticide registration for use on their crops. It is not uncommon for such a process to span over a period of 3 to 5 years. What concerns me is what these farmers do in the interim while they await approval. Many of them are small family farmers that rely on the sale of their crops to survive. Mr. President, they need our assistance.

Chemical pesticides are one means of controlling pests. Other techniques involving biological control and management practices to break the life cycle of pests are also essential. These strategies, referred to as integrated pest management, are the long term approaches to pest control.

Many of Hawaii's farmers already practice many integrated pest management strategies in addition to utilizing chemical pesticides. Through proper regulation, we can insure that chemical application on minor crops continues to maintain standards that are environmentally sound while insuring effective pest control and producing hardy and safe agricultural products. Mr. President, I believe that the measure we are introducing today will accomplish this important objective.

In closing, I would like to acknowledge the major role that my late colleague, Senator Spark Matsunaga played in the drafting of this legislation.

Mr. President, I urge my colleagues to support this important measure.

Mr. ADAMS. Mr. President, I rise as an original sponsor of the Minor Use Pesticide Act of 1990. This legislation, consisting mainly of technical amendments to the Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA], attempts to address a crisis we face today in the area of minor crop and minor use pesticides.

The term "minor crops" and "minor uses" refer to limited acreage crops or specific pesticide uses on crops where the market potential for a crop protection chemical is very small. Minor crops are not minor in any other sense of the term. In my State, where agriculture is our largest industry, the Washington State Department of Agriculture estimates more than 90 percent of our crops fall into this category.

In 1988, Congress, responding to concerns that many older registrations needed scientific reevaluation, passed FIFRA amendments requiring EPA to reregister all existing registrations for pesticide use. The impact of reregistration on registrations of minor use pesticides is expected to be severe. This process will be very expensive. Many chemical manufacturers are expected to choose simply not to renew their minor use registrations, because the market for the product is not worth the expense.

The problem we face is not that some older products may now be judged unsafe and pulled from the market. That is what the reregistration process is for. If a chemical cannot meet our safety standards it should not be used. What concerns me are situations where safe products become unavailable for our farmers, often without notice or the chance to develop alternatives.

The intent of this bill, therefore, is to make sure those most immediately affected by reregistration—America's minor crop farmers—are given notice that chemical products they use may be affected by this process, and given an opportunity to see that the pesticide goes through the reregistration process. I believe this bill does this in ways consistent with FIFRA's overall public safety goals.

First, current law says chemical manufacturers can decide not to reregister through what is called voluntary cancellation, with no notice to affected farmers. The bill would require EPA to determine if any voluntary cancellation request would affect minor crop farmers. If so, EPA would have to notify affected growers, and could not approve the request for 90 days.

Second, in a case where a qualified grower group arranges with a chemical manufacturer to become a third-party registrant, and assume responsibility for the registration, the bill requires EPA to approve the transfer unless EPA determines that continued use of the pesticide would pose an unreasonable adverse effect on the environment. If the transfer is approved, EPA cannot cancel or amend it for 180 days. To further facilitate such transfers, the bill permits growers to enter into voluntary agreements with chemical manufacturers to waive liability

for crop damage. This provision is not intended to affect any other type of liability.

This provision gives a grower group the opportunity to take a pesticide through the reregistration process when the chemical manufacturer decides not to do so. The bill provides that the new registrant for a pesticide remains responsibile for pending data requirements existing at the time of the transfer.

Next, the bill clarifies that EPA cannot require residue data on pesticides registered for minor use in geographic areas where EPA feels use of the pesticide is not likely. The bill also extends EPA's existing discretionary authority to waive fees for any reregistration exclusively dealing with minor uses. EPA would now waive fees for the minor use portion of a registration even if that registration included major uses as well.

The bill also addresses the Inter-Regional Research Project No. 4, the IR-4 Program. This program, annually funded as a special grant, is designed to support registrations of pesticides for minor crops through the generation of required data. In the Pacific Northwest, IR-4 work is done at Oregon State University, at the ARS lab in Yakima, and hopefully soon at the new Food and Environmental Quality Lab I have proposed for Richland, WA.

IR-4 is an excellent program, but it does not have the resources to meet the demand for minor crop pesticide data created by the reregistration process. I understand the administration is considering increasing its inadequate funding request, and I certainly encourage that effort. This bill is designed to make permanemt IR-4's existence as a Federal program. The bill establishes the program, authorizes $25 million in funding, and expands its existing mission.

In addition, the bill directs EPA and USDA to complete a study identifying pests that affect minor crops, identifying chemical control measures for such pests, and giving the status of the search for alternative means of control.

Finally, I would like to express my gratitude for the contribution made to this legislation by my late colleague, Senator Spark Matsunaga of Hawaii. His efforts on behalf of the minor crop growers of this State were just one more reason why all of us here in the Senate miss him very much.

Mr. President, I look forward to discussing these proposals with other members, farmers, consumers, environmental groups, and chemical manufacturers.

By Mr. PRYOR (for himself, Mr. ADAMS, Mr. BUMPERS, Mr. BURDICK, Mr. CONRAD, Mr. EXON, Mr. KERREY, and Mr. KOHL):

S. 2605. A bill to amend title XIX of the Social Security Act to provide mechanisms to control Medicaid drug prices while assuring that beneficiaries receive quality medical care, physicians' prerogative to prescribe is protected and the role of pharmacists is enhanced; to the Committee on Finance.

PHARMACEUTICAL ACCESS AND PRUDENT PURCHASING ACT OF 1990

Mr. PRYOR. Mr. President, today I am formally introducing legislation to reduce prescription drug prices purchased by the $3.5 billion Medicaid Program, the Government's health insurance safety net for the poorest Americans. My bill is called the Pharmaceuticals Access and Prudent Purchasing Act of 1990.

Mr. President, as I discussed on the floor just 2 days ago, the country faces a smoldering crisis of affordability that is about to become an inferno. The staff at the Senate Special Committee on Aging tell me they are getting calls from other Senators' and Representatives' offices every day, asking what they can do to answer their constituents' letters about high drug prices. Everyone of us in this Chamber has received complaints from sick elderly and poor people, States, physicians, pharmacists, and insurers about skyrocketing prescription drug costs.

The only representative of the health care industry satisfied with the current sysem appears to be the drug manufacturers. We must take steps to stop or at least control the unacceptable trend of prescription drug price increases tripling all other price increases.

My answer to this crisis has been to study the best business practices already being used by hospitals, HMO's and a handful of Federal Government agencies to negotiate lower drug prices for the American people. What I found was that the Department of Veterans Affairs, hospitals, and HMO's were obtaining 30 to 40 percent discounts under what the State Medicaid programs are paying. While no one would begrudge a nonprofit hospital serving indigent patients a discount, how can anyone argue that the Medicaid Prescription Drug Program serving millions of poor people should not have access to at least the same or similar discounts?

I have, therefore concluded, as I hope and believe many of my colleagues will, that there is absolutely no reason why the financially destitute Medicaid Health Insurance Program should not also directly negotiate with the drug companies. However, despite the valiant efforts of States to do just that, the drug manufacturers have almost without exception denied them reasonable prices for desperately needed medications. It is time that we assist our State governments in getting the manufacturers to sit down at the bargaining table.

The Pharmaceuticals Access and Prudent Purchasing Act would facilitate negotiations while also reversing the common Washington presumption that our first recourse should be to tell the States how to run their programs. As a former Governor, I have worked for months to craft a bill that gives States both the necessary information and the incentives to negotiate with drug manufacturers while also improving the likelihood that the drug companies will finally take the States seriously when they ask to negotiate.

The legislation has what I call an "or else" clause that will take effect only if the combination of incentives and pressure on the industry fails. The "or else" clause provides that if the drug manufacturers continue to ignore the States' requests for a fair deal, the States will join together in big buying groups that the drug companies literally cannot afford to ignore. I hope that is never going to be necessary, but history teaches that most of the drug companies don't do anything for anyone that they don't have to.

Many of my colleagues on the Finance, Aging and Labor Committees, I gather, have been subjected to a barrage of lobbying activity by the drug companies about this bill that I am introducing today. In all the years I have been in the Senate, I have never seen such an extensive lobbying campaign against an idea that has yet to be formally introduced.

The drug manufacturers have all sorts of arguments against this bill. However, the only argument the industry doesn't come to the Hill with is the one reason why they are here: my legislation might slightly reduce their excessive profits by asking them—like everyone else—to share in the burden of Medicaid cost containment. To assist my colleagues in sorting out truth from the fiction that the manufacturers have been circulating, I have prepared a brief question and answer document that responds to the manufacturers outlandish arguments against my bill. In addition, I believe it is important to note that the very organizations who represent the interests of Medicaid recipients have not only rejected the manufacturers unprecedented lobbying efforts but have written me letters of support.

In the interest of time, I will not go through the numerous red herring arguments the manufacturers have raised. However, I would like to address the one argument that most of us have heard time and time again on the drug pricing issue. We have all heard how efforts to control drug prices will kill the drug industry and its investment in research and development. They say that my bill will choke the golden goose or research and development that may someday produce a cure for Alzheimer's disease or AIDS, or cystic fibrosis. Perhaps we should expect such rhetoric from those who job it is to rally their legions of lobbyists. But what do cooler heads say about the impact of my bill?

One respected Wall Street investment analysis house recently conclud-