syngenta

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Document Processing Desk
Office of Pesticide Programs (H7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Jim Tompkins, Team 25

SUBJECT: Syngenta Crop Protection, Inc., Additional Data and Information Relevant to *Memorandum from Nicole Zinn, Biological Analysis Branch, EPA and Jin Kim, Biological and Economic Analysis Branch, EPA to Hope Johnson, Registration Division, EPA, Paraquat Assessment, D323223, dated 12-7-05.*

Dear Mr. Tompkins:

Syngenta is submitting new data and information validating the improvement in human safety of the Inteon formulation of paraquat. These data provide an important addition to the factual record necessary regarding BEAD's analysis of the benefits and risks of the new paraquat safety standard set by the Inteon formulation. Syngenta requests that this new data and information be evaluated and acknowledged in a follow up to the Dec. 7, 2005 BEAD assessment. Attached to this letter for the Agency's review are three documents:

(A) An abstract summarizing findings following intensive observational monitoring in Sri Lanka before and after the introduction of an Inteon formulation. The abstract was prepared for a presentation in August 2006 and the results indicate a statistically significant improvement in oral toxicity in humans following ingestion of paraquat formulated with the Inteon® technology compared to a non-Inteon formulation available in Sri Lanka before the introduction of the Inteon formulation;

(B) A treating physician's case report of a person in the United States who survived the intentional ingestion of a large amount of Gramoxone Inteon; and

(C) Descriptions of fatal incidents involving unintentional human ingestion of the non-Inteon formulation from 2000 to 2005 that were reported to the poison control center, PROSAR.

Syngenta will submit within the next few weeks comprehensive comments on the December BEAD analysis, including additional factual information that is critical to BEAD's assessment of the risks and benefits of Inteon.

The following new data and information provided with this letter provide BEAD with important new and more complete information to undertake this analysis with a much higher level of reliability.

(A) Large scale monitoring data on the reduced oral toxicity of Inteon in humans following ingestion are now available. An observational monitoring program underway before and after the introduction of an Inteon formulation in Sri Lanka shows a significant improvement in survivability following ingestion of Inteon compared to the non-Inteon formulation. The results of this intensive monitoring program will be presented in a scientific paper at the Asia Pacific Association of Medical Toxicologists' Congress (to be held in Sri Lanka from 6 - 8 August, 2006). The submitted abstract is now available and is attached (Attachment A). The monitoring program demonstrates a statistically significant improvement in survivability following ingestion (primarily intentional ingestion at higher volumes) of Gramoxone Inteon vs. non-Inteon paraquat. Of note, the Inteon formulation available in Sri Lanka was found to have a separation problem after introduction compromising the full potential for improvement in safety. The separation was caused by addition of wetters (adjuvents) to the Sri Lankan formulation. The U.S. formulation does not contain wetters, and, therefore, offers even greater promise for improving survivability following ingestion.

(B) A recent paraquat ingestion incident in the United States followed up with physician monitoring and reporting also validates the improved toxicity of Inteon. As explained in the enclosed case report from Fermin Barrueto, Jr., M.D. (Attachment B), an individual intentionally drank a large volume (approximately 4 ounces) of Gramoxone Inteon, the new formulation registered in the U.S. The individual was treated and survived. The patient would have most likely died if a non-Inteon formulation were ingested, since 4 ounces of formulation is greater than 10 times the typical lethal dose of a non-Inteon paraquat containing formulation. There was also an incident reported last month [submitted to U.S. EPA under FIFRA § 6(a)(2)] where an individual intentionally drank a large volume (exact amount unknown) of non-Inteon Gramoxone in Canada. The individual died on the same day of ingestion.

(C) Paraquat incident data collected from the poison control center PROSAR is more up-to-date than the data analyzed by BEAD and indicates a significantly higher number of fatal outcomes resulting from unintentional ingestion of the non-Inteon formulation. It should be noted that all of these incidents involved the non-Ineon formulation of paraquat, which is no longer being produced or sold by Syngenta in the U.S. In the benefits section of the assessment, BEAD presented a quantitative valuation of the cases of unintentional deaths and illness that may be potentially avoided as a result of paraquat reformulation. BEAD obtained the incident data from a variety of sources (e.g., TESS database), adjusting these numbers for potential under-reporting and area coverage, and provided the estimated number of cases. Based on their analysis, BEAD estimated the total number of fatal unintentional cases to be 2.4 per year; they indicated that 6 deaths were reported over an 11-year period.

An analysis of PROSAR data for the 6 year period 2000 – 2005 revealed 29 actual cases of paraquat poisoning in the US. Eleven (38%) of these were classified as deliberate (intentional) and 18 (62%) as accidental. The accidental cases included people ingesting material decanted into drink bottles, a man denying a suicide attempt, someone ingesting what he thought was tobacco spit, a doctor suspecting paraquat poisoning without confirming paraquat exposure and a 15 month old child drinking from a container in the back of a car. In 2 accidental cases there was

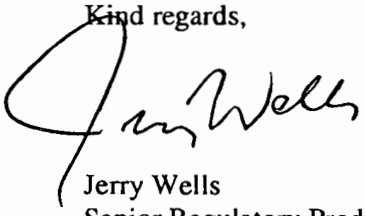
predominantly topical exposure. Very often the information obtained was from a third party and not the patient themselves and therefore, factual information is limited and in many cases detailed hospital records were not available. Ten of eleven people who intentionally ingested non-Inteon paraquat (91%) died and 8 of the 16 people who accidentally ingested non-Inteon paraquat (50%) died as a result (see Attachment C).

Based on Syngenta's analysis of the PROSAR data, there were 8 cases of unintentional ingestions resulting in death since the formation of Syngenta (2000-2005) calculating to an average of 1.3 deaths per year over this 6 year period. This figure is more indicative of the recent trend and significantly higher than the 0.6 deaths per year (1993-2003) used by BEAD in their assessment. Using this higher number of deaths and the BEAD analysis methodology taking into account potential under-reporting and coverage, the estimated number of unintentional deaths per year would be calculated to be 5.9 [(8 deaths/0.911)*4]/6 years. The Total Value in Table 7 of BEAD's assessment would then be $37,878,000 (value of a statistical life of $6,420,000 X 5.9 deaths per year).

Syngenta requests that the Agency evaluate this important new data and information and acknowledge in a follow up document to the BEAD analysis that 1) there is now scientific evidence available that the Inteon technology has been shown to reduce oral toxicity to humans and 2) to revise the upper benefit from $15,443,322 to $37,878,000. As noted above, the benefits of Gramoxone Inteon should also include the prevention of deaths in some portion of the intentional ingestions. Therefore, the benefits even after the adjustment suggested above are still likely significantly understated as BEAD's analysis only included unintentional incidents.

Thank you for your consideration of this new and important data and information. If you have any questions concerning the data and information please contact me at 336-632-6324.

Kind regards,



Jerry Wells
Senior Regulatory Product Manager

Attachments

ATTACHMENT A

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.

ATTACHMENT B

(Email from Fermin Barrueto Jr., MD, Assistant Professor – Department of Emergency Medicine, University of Maryland School of Medicine, Medical Toxicologist)

A Severe Paraquat Ingestion that Survived

A 27 year old man, in a suicide attempt, ingested ½ a cup (4 ounces) of Gramoxone® (Syngenta), a 43% 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; CO_2, 22 mmol/L; BUN, 57 mg/dL; Creatinine, 6.0 mg/dL; Ca^{2+}, 9.2 mg/dL; Phosphorous, 3.5; Mg^{2+}, 2.0 mg/dL; SGOT, 24 U/I; SGPT, 78 U/I; 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; PCO_2 36 mmHg, PO_2, 56 mmHg; HCO_3, 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 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.

ATTACHMENT C

Fatal Unintentional Incidents Involving Non-Inteon Paraquat Formulations

September 2005. Apparently a paraquat-containing product was poured into a soft drink bottle and given to a neighbor, and the patient consumed an unknown amount. The family apparently reported the ingestion was accidental, however other reports indicated the product was intentionally ingested along with an organophosphate insecticide. The caller did not know name of two products nor the concentrations or amounts ingested. Paraquat was detected in the patients urine. The patient died as a result of ingesting paraquat.

June 2005. On 06/06/05, Syngenta was notified that a 48 year-old man accidentally consumed the pesticide through misuse of the product on June 3, 2005. The patient initially thought the glass containing paraquat contained tobacco spit, and he did not immediately seek medical attention. He subsequently developed symptoms that were consistent with paraquat ingestion. The patient eventually expired on June 15, 2005.

December 2004. Syngenta was notified that a homeless man moved in with his ex-wife and her new husband and then became ill. He presented to VA hospital on 12/14/04 and was diagnosed with atypical pneumonia and hypoxia. Symptoms did not respond to standard therapy and he had deteriorating condition required intubation. The patient's lung was biopsied and honeycomb effects were noted. Poison Center Toxicologists were involved as of 12/28/05 and suspicion of paraquat ingestion was raised, although no oral or GI lesions or corrosive injuries were present. The patient expired on 12/31/04, and no plasma or urine samples were retained; therefore, paraquat analysis was not possible. It is unclear whether or not the individual was actually exposed to paraquat or how the exposure occurred, if at all.

September 2004. A chemist in the clinical lab at Presbyterian Hospital in Dallas, Texas, called regarding a patient that the treating physician suspected was exposed to Paraquat. The chemist did not have any details of how the patient was exposed; he only knew that it was an adult patient, and the treating physician requested a test for paraquat. Very little information was obtained about this case because the treating physician would not return the calls. Based on the sparse information obtained, it appears that the patient was a cattle rancher, and his family denied that this was a suicide attempt. He presented to emergency room seriously ill and expired in hospital due to pulmonary fibrosis and pulmonary emboli. A specific cause for these complications has not been identified. A 2 1/2 ml sample of post mortem whole blood was submitted for analysis however this may not be a sufficient volume for paraquat analysis. Furthermore, the blood sample was collected post-mortem, and, considering the rapid half-life of paraquat in blood, it is unlikely paraquat concentrations will be below the level of detection.

March 2003. A 49 year-old male apparently worked in the agricultural business and obtained a small volume of the Gramoxone from a farmer to use around his yard at home. He reported that he was cleaning out his garage, found the container containing Gramoxone, and proceeded to pour Gramoxone into a coffee cup; it is not clear why he decanted the Gramoxone. He reported that he mistakenly drank from the cup containing the Gramoxone instead of his coffee, which was apparently nearby. He indicated that he ingested one to two swallows (up to 1/2 cup) and immediately rinsed and spit with water after he discovered his mistake. Within an hour of exposure, he developed abdominal pain and vomiting prompting him to go to the local emergency room.

The patient was treated with activated charcoal and started on IV fluids. He did not receive any supplemental oxygen. Physical exam did not reveal any evidence of corrosive injury to lips or mucosal surfaces in mouth and throat. The patient had multiple episodes of vomiting and initial tests reported serum creatinine of 1.0, BUN of 10, and normal lung function. The following morning kidney function decreased (serum creatinine of 3.0 and BUN of 19) but the Chest XRAY was unremarkable. The patient was in no respiratory distress, but continued to complain of abdominal pain and dizziness. On 03/05/2003, a nurse indicated that the patient's kidney function continued to decline. On 3/12/03, it was reported that the patient died.

ATTACHMENT C (Cont.)

November 2002. Reportedly, an individual purchased two 20-ounce bottles (plastic bottles with screw-caps) of Pepsi from a local convenience store, and she placed them in her refrigerator at her residence. Her brother opened one of the two bottles, and took one sip (exact amount ingested unknown). He immediately noted that it didn't taste like Pepsi. The patient had several subsequent bouts of vomiting and was taken to Appalachian Medical Center that evening or the following morning. He was in "critical condition" in the emergency room until he died.

FDA criminal investigator shared a few of the facts of the incident. It appears that the Pepsi bottles containing the paraquat were not purchased at the local convenience store as previously suggested. Apparently, the nephew of the patient owned a local farm, which is located near the convenience store where the Pepsi's were allegedly purchased. One of the farm hands at the nephew's farm apparently reported that he filled two Pepsi bottles with Gramoxone Max and gave them to the patient's brother-in-law. It is surmised that the brother-in-law brought the Pepsi bottles home where the patient accidentally ingested the product. FDA classified the incident as an isolated event involving the use of an inappropriate container for storing an herbicide.

October 2002. A 66 year-old female operated her own greenhouse, and a neighbor needed help with weed control. She retrieved an old container of paraquat (29.9% Ortho Paraquat) from storage and put on her counter to give to the neighbor the next day. During the night the patient allegedly woke up to get some cough medicine, which was next to product. On 10/02/02 (1 a.m.), the patient allegedly drank a couple sips of paraquat by accident as she reached for her coffee. She was seen at the emergency room approximately 20 hours after ingesting the product. The treating physician reported that she had oral and esophageal burns, had WBC of 20,000, was hypokalemic, in renal failure and acidotic. The patient died on 10/04/02.

April 2000. On 04/10/00, a paraquat-containing herbicide was stolen from the workplace, decanted into a sports drink container, and placed in the back seat of a car. A 15 month-old child picked up the container and ingested an unknown quantity. The child was put in the intensive care unit and had evidence of oral ulcerations. The child died after 11 days in the hospital.