Status of Paraquat in Nigeria:

WHY A BAN IS NECESSARY

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About the Cassava Weed Management Project

The Cassava Weed Management Project also known as the Sustainable Weed Management Technologies for Cassava Systems in Nigeria ended its 5th year in 2018, assessing sustainable weed management technologies for cassava-based farming systems in Nigeria. The project is currently in an extension phase under the African Cassava Agronomy Initiative (ACAI) and is seeking to find solutions to the labor-intensive weeding usually performed by women and children, and also piloting digital extension in Nigeria and Tanzania.

In the last 5 years, the project reached 74,000 farmers through training and farmer-to-farmer contact, 75,000 through print materials, and 222,000 through social media. Radio and Television with viewership of over 2 million were used to air the project's extension toolkit known as the Six Steps to Cassava Weed Management.

Partners in the project included the National Root Crop Research Institute, Umudike; University of Agriculture, Makurdi; Federal University of Agriculture, Abeokuta and private and public sector extension partners including the Agricultural Development Programs in Abia, Benue, Ogun and Oyo States in Nigeria.

Should Paraquat be Used or Banned in Nigeria?

Historical background and herbicide activity

Development

Paraquat (PQ), with the chemical formula -$C_6H_7N)_2]Cl_{2)}$ and chemical name N,N′-dimethyl-4,4′-bipyridinium dichloride, is an organic compound classified as a viologen, which is an active redox-active heterocycle. PQ was first synthesized in 1882, although its herbicidal properties were not recognized until 1955. PQ as a herbicide was first manufactured and sold by ICI in 1961 as a broad-spectrum non-selective herbicide and today is one of the most commonly used herbicides in over 100 countries and over 70 crops (paraquat.com; Brown et al. 2004; Bromilow 2003; Dinham 2004).

The active ingredient PQ is a non-volatile, white, crystalline solid, melting and decomposing at 300 °C and is extremely soluble in water and practically insoluble in most organic solvents. As a commercial herbicide, PQ is formulated as the dichloride salt.

Mode of action and environmental safety – PQ is a contact (not a systemic) herbicide that is rapidly absorbed by green plant tissue and quickly acts in the presence of both light and oxygen to kill the tissue by rapid desiccation. Only green plant tissue that PQ contacts is killed. PQ has limited to no translocation within a plant because cell death begins within 30 minutes under high light conditions. PQ molecules that enter the plant act in the chloroplast where photosynthesis occurs. In the absence of PQ, chloroplasts absorb light energy and produce reducing energy that in turn is utilized to produce sugars essential for plant growth. PQ targets the electron transport system of photosystem I in the chloroplast and diverts electrons from iron-sulfur centers in photosystem I in the chloroplast and is reduced (redox process), effectively stopping normal photosystem I activity in the plant. There are many biological functions in plants where electron transfer occurs, notably in photosynthesis and respiration. Since PQ is a strong electron acceptor, it interferes with part of the photosynthesis process (photosystem I) in plants accepting electrons from a protein called ferredoxin. The reduced PQ then reacts with O_2 to form free radicals (superoxide [O_2-]) that in turn can generate hydrogen peroxide radicals and both radicals can react with unsaturated fatty acid components of cell membranes. The interaction destroys cell membranes and cell contents leak and mix causing total cell death. The result is the characteristic rapid browning of leaf tissue observed after PQ application. Complete death of the plant occurs within a few days. The rapid plant desiccation allows applicators to observe that PQ is working to kill sprayed weeds (paraquat.com; Brown et al. 2004).

A similar process causes respiratory problems in animals when PQ is ingested. In plants, if PQ is applied in the dark, respiration can be inhibited. This process will be discussed later in this paper relating to concerns about the safety of PQ when used as an herbicide.

Paraquat is effective against all plant tissue to which it is applied, but since it does not translocate, PQ is most effective in killing annual weeds and emerged leaves of perennial weeds but not the perennial underground roots and/or rhizomes. Perennial weeds can regrow after a PQ application (Bromilow 2003).

An important aspect of PQ action is that it is rapidly absorbed within minutes by plant tissue. This rapid absorption eliminates the potential of any lack of efficacy if rain occurs after application. PQ that contacts the soil is rapidly adsorbed to soil particles and deactivated. The soil adsorption/ deactivation does not cause a problem with PQ leaching through the soil or running off into surface water (Bromilow 2003; Brown et al. 2003).

Use in controlling weeds

Paraquat has been on the commercial market since early 1962. Adoption was mainly for contact weed kill in non-crop, rights of ways and in perennial crops where directed sprays could be applied to avoid crop injury. Over the years, its use has increased for site preparation of annual crops, as a solo herbicide or in combination with other herbicides for site prep in no-tillage crops and directed sprays in many crops.

Situation uses – Paraquat is a nonselective, broad-spectrum herbicide used either as a herbicide to kill foliage in sites prior to crop planting (widely used in no-till farming) or as a directed herbicide applied to weeds but not directly applied to susceptible crops by either directed and/or shielded applications. Paraquat has been on the market since the early 1960s and has been used by over 25 million farmers (Brown et al. 2004; Shoham 2013). Paraquat is widely used in the developing world as an aid to weed control and to reduce hand weeding. This use is a major argument to support its continued registration. Although, this is true, other herbicides can also achieve a similar result.

Effectiveness – Paraquat is an effective contact herbicide applied to kill emerged annual weeds and to burn back foliage of perennial weeds. Since it is nonselective, application, especially on annual crops, has to be precise to avoid damaging crops present in the field. PQ has wide use in many perennial crops such as tree fruit, tree nuts, vines, rubber, pineapple, coffee, sugarcane and banana as application to mature bark does not result in crop damage. As mentioned, it has become more widely used in no-till farming as an aid to glyphosate and broadleaf, weed-specific herbicides. Arguments have been made (Bromilow 2003; Brown et al. 2004; Brown et al; 2003; Sholam 2013) that PQ use was a major tool in making no-till farming possible especially since PQ leaves soil stabilizing roots intact and this helps to reduce soil erosion. This argument is not completely true, as worldwide, glyphosate was the primary stimulus for widespread no-till or reduced till agriculture adoption and it is still more widely used in no-till situations than PQ. Glyphosate also leaves roots in the soil to help reduce soil erosion. Paraquat has been widely adopted, especially in Australian agriculture to control glyphosate-resistant weeds. Although, some would argue there are fewer weeds resistant to PQ than other herbicides, worldwide, there are now 24 documented resistant-weed species (6 grass and 18 broadleaf species) to PQ (Preston 2018).

World use

Peak use and patterns of change

Paraquat, like other herbicides, was used increasing from the early 1990s through 2007 when herbicide use started to level off or decrease in the developed world. Since 2007, its use has remained steady with increasing use in the developing world. PQ, as of 2014, was the third most commonly used herbicide in the world after glyphosate and phenoxy herbicides (Zhang 2018). Predictions estimate that PQ will be the fourth most common herbicide by 2020 (Zhang 2018). Use in the developing world has increased since 2007 but its use in the developed world has declined, probably related to its being banned or not reregistered in over 32 countries. The three largest markets for PQ are Brazil, China, and the United States. Approximately 39% of total sales are in South East Asia, 22% in Central and South America, 21% in North America, 6% in Japan, 2% in Africa, and 1% in Australia (Shoham 2013). Adoption has been consistent and continuing due to its unique herbicidal characteristics, which make it a useful weed control agent in a variety of environments. PQ quickly binds to the soil, does not leach or runoff into surface and ground water, and stays where it is applied. PQ can be used in wet highly humid climates, as it is rainfast within minutes of application to plant tissue. PQ is easily applied in perennial crop systems because application to the plants' mature bark is not toxic.

PQ has become important in crops where glyphosate has been applied as it controls many of the weeds that have developed resistance to glyphosate. Many authors have stated that PQ use is important for continued sustainable weed management in world agriculture (paraquat.com; Bromilow 2003, Black et al. 2003).

Concerns with paraquat use

Application requirements. Paraquat is a contact herbicide that is quite effective against most annual weeds, both grasses and broadleaves. The disadvantage is PQ does not kill the underground portion (roots, rhizomes, tubers, etc.) of perennial weeds so they will regrow. When there are repeated flushes and continuing germination of weeds in a growing season, repeat application is necessary to kill new weeds, as PQ has no soil residual activity. Application of PQ requires the use of a surfactant so that the applied spray contacts all portions of the weed foliage and stem to obtain complete kill. PQ is most effective against small weeds and complete coverage and kill of larger weeds is difficult as PQ does not translocate within the plant (Brown et al. 2004).

Application Safety. Paraquat is a widely used herbicide throughout the world in both developed and developing countries but is a highly toxic herbicide (human contact with PQ has been associated with many health problems (see toxicity sections below) and any exposure of the applicator to the concentrated commercial product or diluted spray solution should be avoided. Regulations vary between countries as to the restrictions imposed on how the herbicide can be purchased, handled, applied, and stored. In developed world countries such as the United States, strict requirements exist to minimize applicator and other persons' exposure to PQ. For example, in the United States, all PQ products registered for use are considered "Restricted Use Pesticides" (RUPs), meaning they can only be sold to and used by certified licensed applicators or applicators under their direct supervision. Handling and spraying of PQ requires wearing personal protective equipment when handling, mixing, and applying that includes eye, face, nose, and body protective clothing or safety equipment. These requirements, unfortunately, do not exist in all countries and many developing countries have no specific requirements. In some instances, especially in the developing world, PQ is readily available and easily purchased by anyone, with often no regulations requiring use of protective clothing when handling, mixing, or applying PQ. Since PQ is considered to be, potentially, one of the most dangerous herbicides sold, applicator exposure to PQ could be high if there are no restrictions.

Labels in the USA also specify proper storage, disposal of excess spray material, and empty container disposal. PQ must be stored in its original container and in a locked building. Any excess pesticide spray must be disposed of in an excess chemical storage tank and disposed of in an approved chemical disposal facility. An empty PQ container cannot be reused or refilled. An empty container must be rinsed three times, the rinseate should be placed in the spray tank, and either immediately used during another spray operation or stored in the locked facility until used.

Manufacturers of PQ who sell it for use in managing weeds say that PQ is safe to use and causes no problem to the applicator when applied according to the label recommendations (Brown et al. 2004). Label precautions during PQ use include wearing gloves and eye protection when handling the concentrated product and wearing a long-sleeved shirt, long trousers, and boots when applying (Brown et al. 2004). Additionally, clothes used during application should be washed separately from other laundry and any PQ spray solution touching the skin, eyes or any other part of the body should be thoroughly washed away immediately. Medical personnel should immediately assess any extreme inhalation or ingestion. This argument suggests that when these precautions are used, PQ does not pose any serious health issues to applicators or others.

The problem with this argument, as suggested by Wesseling (2001) and Dinham (2004), is that in the developing world, PQ is often applied under hazardous conditions. These conditions include application under high temperatures and high humidity, no use of protective clothing, faulty spray equipment (especially potentially leaking knapsack sprayers), lack of applicator knowledge about pesticides and their safe use, no readily available washing facilities, no easily available medical treatment facilities, and repeated PQ applications within short timeframes. Such conditions can lead to potentially high levels of PQ exposure for the applicator, especially their skin but also their eyes and nose.

To emphasize the seriousness of potential exposure, a guide to precautions for PQ use and exposure was produced by the US Center for Disease Control and Prevention and is included below as a guide for proper procedures to follow if exposed to PQ. These are precautions to reduce applicator exposure to PQ and are important guidelines regardless of the country where PQ is used and should be the standard requirements for PQ use where its use is allowed.

Facts About Paraquat (US Center for Disease Control, CDC), https://emergency.cdc.gov/agent/PQ/basics/facts.asp)

What is Paraquat?

- PQ is a toxic chemical that is widely used as an herbicide (plant killer), primarily for weed and grass control.
- In the United States, PQ is available primarily as a liquid in various strengths. The US Environmental Protection Agency classifies PQ as "restricted use." This means that only people who are licensed applicators can use it.
- Because PQ is highly poisonous, the form that is marketed in the United States has a blue dye to keep it from being confused with beverages such as coffee, a sharp odor to serve as a warning, and an added agent to cause vomiting if someone drinks it. PQ from outside the United States may not have these safeguards added.

Where Paraquat is found and how it is used

- Paraquat was first produced for commercial purposes in 1961.
- Worldwide, PQ is still one of the most commonly used herbicides.
- In the United States, due to its toxicity, PQ is available for use only by commercially licensed users.

How you could be exposed to Paraquat

- Paraquat is not known to have been used in any terrorist attacks or wars.
- The most likely route of exposure to PQ that would lead to poisoning is ingestion (swallowing).
- Paraquat can be mixed easily with food, water, or other beverages. If the form of PQ that is used does not contain the safeguard additives (dye, odor, and vomiting agent), people might not know that the food, water, or other beverages are contaminated. Eating or drinking PQ-contaminated food or beverages could poison people.
- Paraquat poisoning is also possible after skin exposure. Poisoning is more likely to occur if the skin exposure lasts for a long time, involves a concentrated version of PQ, or occurs through skin that is not intact (skin that has sores, cuts, or a severe rash).
- If it is inhaled, PQ could cause poisoning leading to lung damage. In the past, some marijuana in the United States has been found to contain PQ.

- Licensed applicators of PQ are the people most at risk for exposure.

How Paraquat works

- The extent of poisoning caused by PQ depends on the amount, route, and duration of exposure and the person's health condition at the time of the exposure.
- Paraquat causes direct damage when it comes into contact with the lining of the mouth, stomach, or intestines.
- After PQ enters the body, it is distributed to all areas of the body. PQ causes toxic chemical reactions to occur throughout many parts of the body, primarily the lungs, liver, and kidneys.
- Cells in the lung selectively accumulate PQ likely by active transport.

Immediate signs and symptoms of PQ exposure

- After a person ingests a large amount of PQ, he or she is immediately likely to have pain and swelling of the mouth and throat. The next signs of illness following ingestion are gastrointestinal (digestive tract) symptoms, such as nausea, vomiting, abdominal pain, and diarrhea (which may become bloody).
- Severe gastrointestinal symptoms may result in dehydration (not enough fluids in the body), electrolyte abnormalities (not enough sodium and potassium in the body), and low blood pressure.
- Ingestion of small to medium amounts of PQ may lead to development of the following adverse health effects within several days to several weeks:
  - » Heart failure, kidney failure, liver failure, lung scarring.
- In general, ingestion of large amounts of PQ leads to the following signs/symptoms within a few hours to a few days:
  - » Acute kidney failure, confusion, coma, fast heart rate, injury to the heart, liver failure, lung scarring (evolves more quickly than when small to medium amounts have been ingested), Muscle weakness, pulmonary edema (fluid in the lungs), respiratory (breathing) failure, possibly leading to death, seizures.
- Showing these signs and symptoms does not necessarily mean that a person has been exposed to PQ.

Long-term health effects

- If a person survives the toxic effects of PQ poisoning, long-term lung damage (scarring) is highly likely. Other long-term effects may also occur, including kidney failure, heart failure, and esophageal strictures (scarring of the swallowing tube that makes it hard for a person to swallow).
- People with large ingestions of PQ are not likely to survive.

How you can protect yourself, and what you should do if you are exposed to PQ

- Because ingestion is likely to be the primary route of exposure, if poisoning is suspected, avoid any further ingestion and seek medical attention immediately.
- Pre-hospital therapy may include oral administration of activated charcoal or Fuller's earth to bind ingested PQ.
- If you think you may have been exposed to liquid PQ on your clothes or body, remove your clothing, rapidly wash your entire body with soap and water, and get medical care as quickly as possible.

» **Removing your clothing:**

- Quickly take off clothing that has liquid PQ on it. Any clothing that has to be pulled over the head should be cut off the body instead of pulled over the head.
- If you are helping other people remove their clothing, try to avoid touching any contaminated areas, and remove the clothing as quickly as possible.

» **Washing yourself:**

- As quickly as possible, wash any liquid PQ from your skin with large amounts of soap and water. Washing with soap and water will help protect people from any chemicals on their bodies.
- If your eyes are burning or your vision is blurred, rinse your eyes with plain water for 10 to 15 minutes. If you wear contacts, remove them and put them with the contaminated clothing. Do not put the contacts back in your eyes (even if they are not disposable contacts). If you wear eyeglasses, wash them with soap and water. You can put your eyeglasses back on after you wash them.

» **Disposing of your clothes:**

- After you have washed yourself, place your clothing inside a plastic bag. Avoid touching contaminated areas of the clothing. If you cannot avoid touching contaminated areas, or you are not sure where the contaminated areas are, wear rubber gloves or put the clothing in the bag using tongs, tool handles, sticks, or similar objects. Anything that touches the contaminated clothing should also be placed in the bag. If you wear contacts, put them in the plastic bag, too.
- Seal the bag, and then seal that bag inside another plastic bag. Disposing of your clothing in this way will help protect you and other people from any chemicals that might be on your clothes.
- When the local or state health department or emergency personnel arrive, tell them what you did with your clothes. The health department or emergency personnel will arrange for further disposal. Do not handle the plastic bags yourself.

- For more information about cleaning your body and disposing of your clothes after a chemical release, see "Chemical Agents: Facts About Personal Cleaning and Disposal of Contaminated Clothing(https://emergency.cdc.gov/planning/personalcleaningfacts.asp)".

How Paraquat exposure is treated in the hospital

After a patient is admitted due to PQ poisoning, initial therapy consists of removing the PQ from the body (decontamination) and preventing further absorption by oral exposure through using activated charcoal or Fuller's earth. Nasogastric suction may be considered within 1 hour after ingestion. Supportive care measures such as intravenous fluids (fluids given through a needle inserted directly into a vein), medication to help with breathing and to raise low blood pressure, a ventilator to support breathing, and possibly dialysis for kidney failure are all possible treatments. Administration of excessive oxygen is avoided because it may worsen PQ toxicity. No proven antidote or cure exists for PQ poisoning when orally ingested.

> This above CDC document is useful to establish a starting point for a more thorough discussion about potential health effects of PQ to applicators and others.

Toxicity Classifications for PQ from Various International Organizations

World Health Organization (WHO) – Class 2 Moderately Hazardous

European Union (EU) – Very toxic by inhalation, toxic in contact with skin and if swallowed, danger of serious damage to health by prolonged exposure, irritant to eyes, respiratory system and skin.

United States Environmental Protection Agency (USEPA) – Acute toxicity by inhalation – category 1, highly toxic, acute toxicity from oral intake – category II, moderately toxic, systemic toxicity from dermal absorption – Category III, slightly toxic, eye irritation – Category II, moderate to severe, skin irritation – Category IV, minimal

Acute Toxicity – EC (2003) stated PQ is very toxic by inhalation, toxic in contact with skin, and if swallowed, an irritant to eyes, respiratory system, skin, and a danger to health by prolonged exposure. Common exposure symptoms include burns to the mouth, acute respiratory distress, loss of appetite, abdominal pain, thirst, nausea, vomiting, diarrhea, giddiness, headache, fever, muscle pain, lethargy, shortness of breath, and rapid heartbeat.

California Environmental Protection Agency (CA EPA) – PQ can penetrate the nervous system, is a neurotoxin, and impacts brain functions. Exposure to PQ even in relatively low doses, during critical periods in childhood may adversely affect the development of brain functions.

Toxicity Information from USEPA (Lethal Doses) – LD50 is the dose that kills 50% of test animals and this varies considerably) (http://wildpro.twycrosszoo.org/S/00Chem/ChComplex/PQ.htm)

Highly toxic; EPA toxicity class I

- **Acute toxicity:** Highly toxic by ingestion. Reported oral LD_{50} values of 110 to 150 mg/kg in rats, 50 mg/kg in monkeys, 48 mg/kg in cats, and 50 to 70 mg/kg in cows.
- The toxic effects of PQ are due to the cation, and the halogen anions have little toxic effects.
- Dermal LD_{50} in rabbits is 236 to 325 mg/kg (indicative of moderate toxicity by the dermal route).
- Inhalation LC_{50} (four hour inhalation) is greater than 20 mg/L for the technical grade of PQ.
- Causes skin and eye irritation in rabbits (severe for some of the formulated products); has caused skin sensitization in guinea pigs in some formulations.
- Effects due to high acute exposure to PQ may include excitability and lung congestion, which in some cases leads to convulsions, incoordination, and death by respiratory failure.
- If swallowed, burning of the mouth and throat often occurs, followed by gastrointestinal tract irritation, resulting in abdominal pain, loss of appetite, nausea, vomiting, and diarrhea.
- Other toxic effects include thirst, shortness of breath, rapid heart rate, kidney failure, lung sores, and liver injury.
- Some symptoms may not occur until days after exposure.
- Persons with lung problems may be at increased risk from exposure.
- Many cases of illness and/or death have been reported in humans.
    - Estimated lethal dose by ingestion for PQ in humans is 35 mg/kg.
    - Maximum of 3.5 mg/hour could be absorbed through the dermal or respiratory route without damage.

- » Biphasic toxic action after ingestion, with initial gastro-intestinal tract irritation and renal and hepatic toxicity. One to two weeks later development of pulmonary lesions due to destruction of alveolar pneumocystis.
- » Toxicity is enhanced by deficiency in vitamin E/selenium, high oxygen and low tissue levels of glutathione.

- **Chronic toxicity:**
  - » Repeated exposures may cause skin irritation, sensitization, or ulcerations on contact.
  - » Rats showed no effects after being exposed for 2 years to PQ at doses of 1.25 mg/kg/day.
  - » Dogs developed lung problems after being exposed for 2 years at high doses (above 34 mg/kg/day).
  - » In a study of 30 workers spraying PQ over a 12-week period, approximately one-half had minor irritation of the eyes and nose.
  - » Of 296 spray operators with gross and prolonged skin exposure, 55 had damaged fingernails as indicated by discoloration, nail deformities, or loss of nails.
- **Reproductive effects:**
  - » No adverse reproductive effects reported in a long-term rat study at doses up to 5 mg/kg/day.
  - » PQ dichloride injected intraperitoneally at 3 mg/kg/day on days 8 to 16 of gestation increased fetal mortality in rats.
  - » Hens given high levels of PQ in their drinking water for 14 days produced an increased percentage of abnormal eggs.
  - » PQ is unlikely to cause reproductive effects in humans at expected exposure levels.
- **Teratogenic effects:**
  - » The weight of evidence suggests that PQ does not cause birth defects at doses which might reasonably be encountered:
    - Offspring of mice dosed with high doses of PQ during the organ-forming period of pregnancy had less complete bone development than the mice given lower doses
    - Offspring of rats given similar treatment showed no developmental defects at any dose, but fetal and maternal body weights were lower than normal.
    - Other studies of PQ using rabbits and mice have shown no teratogenic effects.
- **Mutagenic effects:**
  - "PQ has been shown to be mutagenic in microorganism tests and mouse cell assays. It was unclear what levels of exposure are necessary to produce these effects."
- **Carcinogenic effects:**
  - » The evidence regarding carcinogenic effects of PQ is inconclusive:
    - Mice fed PQ dichloride for 99 weeks at high levels did not show cancerous growths.
    - Rats fed high doses for 113 (male) or 124 weeks (female) developed lung, thyroid, skin, and adrenal tumors.

- **Organ toxicity:**
  - » PQ affects the lungs, heart, liver, kidneys, cornea, adrenal glands, skin, and digestive system.
- **Fate in humans and animals:**
  - » PQ is not readily absorbed from the stomach and is even more slowly absorbed through the skin.
  - » Oral doses of PQ in rats are excreted mainly in the feces, while PQ injected into the abdomen leaves through urine.
  - » In the stomach and gastrointestinal tract, PQ metabolites may be more readily absorbed than the parent compound, but their identities and toxicities are unknown.
  - » PQ may concentrate in lung tissue, where it can be transformed to highly reactive and potentially toxic forms.
  - » Farm animals excreted over 90% of the administered PQ within a few days in one study. The compound was slightly absorbed and metabolized in the gastrointestinal tract. Milk and eggs contained small amounts of two PQ metabolites.
- **USEPA** (1997) reported the following adverse effects from subchronic toxicity testing:
- Oral – increasing lung weight, large lesions in lungs, alveolar collapse, shortness of breath, harsh rattling noises when breathing, slow or irregular heartbeat, decreased food intake, and weight loss.
- Dermal – minimum to severe inflammation, pre-cancerous cell proliferation, thickening, ulceration and exudation, and decreased weight of testes.
- Inhalation – nasal discharge, epithelial cell proliferation, ulceration, necrosis and inflammation of larynx and in lungs thickening of the alveolar walls, and aggregation of white blood cells.

Precautions and restriction concerning PQ purchase and use in some parts of the world

Paraquat is available primarily as a liquid in various strengths. The US Environmental Protection Agency (USEPA) classifies PQ as "restricted use" (RUPs), which means it, can only be sold to and used by certified licensed applicators (and applicators under their direct supervision). There are no homeowner uses and no products registered for application in residential areas. There are also strict requirements for use of personal protective clothing, respirators when mixing, and applying PQ to reduce any potential for exposure to toxic levels of the herbicide. Because PQ is highly poisonous, the form marketed in most developed world countries has a blue dye to keep it from being confused with beverages such as coffee, it contained a sharp odor component to serve as a warning agent, and has an added component that causes vomiting if someone ingests PQ. PQ sold in the developing world may not have these safeguards added to the commercial product and that is a concern regarding its safe use. A corollary to the RUP and safety requirements in the developed world is that all pesticide applicators have to be tested and licensed in order to legally apply pesticides. Additionally, due to health concerns regarding PQ use, is now banned or restricted in over 32 countries in the world.

Arguments for and against PQ use in agriculture

The scientific and popular literature has many papers that provide arguments for and against the use of PQ in weed management, especially in agriculture. Outlooks on Pest Management has published a series of articles in 2004 (Copping 2004; Brown et al. 2004; Dinham 2004), in 2005 (Trewavas 2005), in 2007 (Editorial 2007; 2011) and in 2013 (Shoham 2013) concerning the pros and cons of PQ use, its importance

economically, and its potential safety or toxicity and danger to humans. These articles and two monographs on PQ published by the Pesticide Action Network (Watts 2011 and Isenring 2017) provide some of the best information available on how PQ is used in agriculture, why it has been a valuable weed management tool, and why there are major concerns regarding PQ toxicity, especially the safety and health concerns to the applicator.

Many of the opinions in the cited articles are based on PQ as a useful and safe herbicide (Brown et al. 2004; Trewavas 2005; Shoham 2013) or against PQ because of its potential toxicity to humans (Dinham,2004; Watts 2011; Isenring 2017). There are numerous scientific papers (cited below) reporting research on PQ concerning its effectiveness as an herbicide and the potential health problems PQ poses to humans through exposure.

The benefits (in general) for effectiveness of PQ in weed management in agriculture include its rapid non-translocated action in killing weeds, its usefulness for effective weed management, soil conservation in no-till agriculture, and how PQ results in more sustainable agriculture. PQ has a distinct advantage over most postemergent herbicides for weed control as it only kills plants that it is applied to, is not volatile (stays where it is applied), and it quickly binds (essentially irreversibly) to any soil it contacts making it a minimal problem for leaching or runoff into surface or groundwater. Arguments include that PQ is a cost-effective herbicide and claims of harmful health effects are overstated and often inaccurate (Brown et al. 2004; Cook et al. 2016). Proponents of PQ use agree that it can cause some minor skin irritation but when properly used, PQ poses no health problems. Proponents of continued PQ use feel that regulatory agencies have determined it poses minimal problems to the environment or humans (also other animals) and that it is safe when used appropriately and most well-done scientific studies have not convincingly shown negative health effects (Brown et al. 2004). PQ is not available for use due to lack of registration in most of the EU or completely banned in over 32 countries in the world (PAN, 2018). Further, its use is restricted in many countries based on regulatory agencies decisions that PQ use without strict application regulations is not safe.

Opponents of continued PQ use argue it is an extremely toxic chemical that has been shown in short- and long-term exposure studies to be a dangerous herbicide that can damage many body organs that it comes into contact with including lungs, heart, kidneys, spleen, and the central nervous system and can result in multiple organ failure. Effects shown to occur include long-tern acute health problems such as severe dermatitis, secondary burns, and respiratory failure and there is mounting evidence that chronic exposure is linked to development of Parkinson's disease (Parkinson's disease) and other diseases (Dinham 2004; Watts 2011; Isenring, 2017. Both sides acknowledge that direct ingestion of PQ whether accidental or intentional is highly toxic and death can occur even if immediate medical attention is available. There is no known antidote to PQ ingested poisoning.

The general agreement between these opinions is that PQ, if used according to specific guidelines of handling, mixing, and spraying (use of proper protective clothing; well-maintained and calibrated application equipment; applied by trained applicators; and any excess remaining spray solution is properly disposed of) human exposure and overall safety is increased.

The major disagreement between these advocate groups is the overall level of toxic potential of PQ. Most arguments for PQ use suggest it is safe for humans and the environment when used properly and laboratory studies and epidemiology studies do not reflect the actual human exposure doses or minimal long-term health effects (Brown et al. 2004). Additional arguments are that there are no effective alternative herbicides to PQ. The continued availability of PQ is vital to effective and sustainable weed management as a necessary tool for expanded use of conservation (Bromilow 2000 and Black et al. 2003). Further, PQ is vital to farmers in the developing world; it is essential to reduce hand weeding and in alleviating the drudgery of weeding (especially for women and children), allowing children to attend school rather than being needed for work

on the farm (Brown et al. 2004). In addition, PQ advocates argue that the many of the scientific studies conducted showing long-term negative health effects of users are poorly conducted and that if these studies were valid, regulatory agencies would have totally banned PQ use long ago (Cook et al. 2016).

Anti-PQ arguments counter that most of these pro comments are invalid and point out that there are alternative weed management tools available, that many scientific studies show PQ is a toxic herbicide, can cause severe injury or death to humans after exposure, and support the need for a total ban of PQ (Dinham 2004; Watts 2011, Isenring 2017). Watts (2011) and Isenring (2017) cite over 300 research and regulatory publications that show the chemical profile of PQ. This includes its inherent toxicity, how it is used, its possible negative effects to the applicator regarding safety and health (with specific examples), and its negative effect and impacts on the environment and organisms within the environment. These articles discuss PQ status and use profile in the world, information on restrictions or banning of its use, and alternatives for weed management. These papers make a strong case for why regulatory agencies should ban or severely restrict PQ use in agriculture.

A thorough evaluation of PQ toxicity and the many scientific articles that show negative health effects of PQ articles clearly show it is a very toxic herbicide. Improperly used it can result in unacceptable human exposure to the concentrated commercial product and diluted spray tank concentrations. Such exposure is documented in numerous laboratory studies and specific human case studies that demonstrate immediate and potentially long-term harm to humans (see US Center for Disease Control [CDC] document).

One aspect to consider concerning the safety of PQ when applied properly is that in the developed world where PQ is legally approved for use, there are restrictions on handling and application. For example, in the USA it is a restricted use pesticide (RUP). A RUP in the USA can only be purchased and applied by trained and licensed people. In addition, RUPs require that personal protective equipment be worn when handling and applying PQ to minimize any exposure to the compound. These strict purchase and use regulations are enforced. The commercial PQ product sold in the developed world includes a stinking agent, an emetic, and a colored dye so it cannot be mistaken for a soft drink. These restrictions are meant to reduce the possibility of unintentional and often fatal oral ingestion.

The strongest pro argument supporting continued PQ use is that when it is applied as specified by the product label, any exposure to the applicator is minimal and not problematic from a negative health consideration (SCP 2003).

However, in most of the developing world (Nigeria included), these types of requirements do not exist. There is minimal to no training of applicators, PQ can be purchased from street vendors by anyone, there are no requirements for inclusion of safety additives in commercial PQ formulations, there are no requirements for handlers and applicators to wear PPEs, no standards for proper maintenance of spray equipment, and anyone including women and children can apply PQ. All these situations tend to be in opposition to the arguments of PQ manufacturers that if PQ is applied following label requirements, the herbicide is safe. In addition, the list of precautions that are contained in the US CDC document concerning exposure and actions are difficult to follow in many developing world countries. In the developing world, PQ is most often applied under hazardous conditions. These conditions include high temperature and humidity, no use of protective clothing, leaking or poorly maintained knapsack sprayers, lack of adequate washing facilities to remove PQ from skin or readily available medical facilities. Additionally, farmers make repeated applications increasing exposure, there is improper disposal of excess spray solution, poor disposal of used herbicide containers, and storage of pesticides, often in unlocked facilities, which makes safe use of PQ extremely difficult.

Another consideration for applicators using knapsack/backpack sprayers to apply PQ is that in 1997, the USEPA (1997) concluded exposure of applicators to PQ was unacceptable when applied with a knapsack/backpack even when applicators were wearing PPEs. The European Union (EC 2002) stated that applicators

of PQ using knapsack sprayers might exceed the short-term acceptable exposure level by 60 times when PPEs are worn and by 100 times when PPEs are not worn.

Toxicology literature on health effects of PQ

Papers relating to health effects of PQ are numerous. All researchers agree that PQ can be fatal if directly ingested, as 1 teaspoon can be fatal if swallowed, however, this is where scientific agreement on PQ toxicity stops. Supporters of PQ argue the herbicide is safe if used according to label instructions and antagonists argue that PQ exposure is unacceptably high in most application situations of PQ outside the developed world and few to no regulation resulting in unacceptably high levels of PQ exposure. Further, most scientific studies show that chronic and acute PQ exposure can lead to severe health problems in humans. The researched negative effects of PQ exposure have been shown for lungs, liver, kidneys, adrenals, thymus, cardiac and hematolympathic systems, cancer, diabetes, genotoxicity and mutagenicity, endocrine disruption, reproductive and developmental birth defects/teratogenicity, immune system, nervous system, and Parkinson's disease, and many deaths from intentional and accidental ingestion (US EPA 1997, Dere and Polat 2000; IPCS1984: Noriega et al. 2002; Kimura et al. 2007; 2010; Shibata et al. 2010; Webb 1983; Dinham 2004; Watts 2011).

The PQ review paper of Watts (2011) and Isenring (2017) highlight numerous research studies as described below that have implicated PQ exposure in various health problems, both immediate and of a long-term nature to applicators or others exposed to PQ. Other papers discussed below have reported results that do not show a strong correlation with PQ and health problems (Brown et al. 2004; Trewavas 2005; Cook et al. 2016).

Documented effects of negative response of humans from PQ exposure

Eyes – USEPA (1997) – clouding of lens and cataracts in rodent

Skin – No absorption through intact skin (USEPA 1997); can enter damaged skin and some fatalities have occurred.

Applicators after short or long-term dermal exposure can experience many health issues (Soloukides et al. 2007; Popiris et al. 1995; Tungsanga et al. 1983: Smith 1988). Dermal exposure to PQ is generally not fatal as PQ is not easily absorbed by intact skin (Garnier 1995, Wester et al. 1989) but exposure can result in localized lesions and blackened finger and toenails (Bismuth et al. 1982; Fitzgerald et al. 1978; Swan 1969; Hearn and Keir 1971; Howard 1979). Long-term dermal exposure from spills onto applicator clothing that is not removed and remains in contact with skin for an extended time (Garnier 1995; Smith 1988) has resulted in death (Garnier 1995; Smith 1988). Eleven fatalities due to dermal exposure of PQ occurred between 1974 and 1994 (Gear et al. 2001). A death was reported within 3.5 hours from a 0.5% PQ solution which saturated the applicator coming from a leaking backpack (Wesseling 2001). In Thailand a farmer spraying PQ and glyphosate all day using a leaking backpack and not wearing any protective clothing developed a cough, skin disease, lost hair and sight, and died within 3 months (Bartliet and Bjil 2003). Fifteen deaths were reported from PQ exposure to applicators in Costa Rica banana plantations (Wesseling 2001) and in Spain (Peiro et al. 2007; Battaler 2000; Vilaplano 1993).

Studies in Nicaragua on banana plantations showed that of 132 PQ applicators, 53% reported exposure to PQ during mixing and application that resulted in skin rashes or burns, 25% reported epistaxis, 58% reported nail damage, and 42% reported eye splash irritation (Castro-Gutierrez et al. 1997. These researchers also reported a correlation to applicator exposure and subsequent wheezing accompanied by shortness of

breath (Castro-Gutierrez et al 1997. A few reports have shown dermal exposure to PQ and subsequent death (Smith 1988) and from exposure to dilute spray tank PQ concentrations (Wesseling et al. 1997; Athanaselis et al. 1983). Van Wendel et al. (1996) showed Central American banana plantation PQ spray applicators had a high PQ exposure level of 113 mg/kg body weight during normal spray events. Once PQ is internalized, it can affect respiration and hepatic and renal system function (Castro-Gutierrez et al. 1997; Soloukides et al. 2007) and can result in death.

Nose – Inhalation not considered a problem (USEPA 1997). Inhalation can be a problem under certain environments and droplets in the nose can irritate mucosal tissue and cause nosebleeds (Wesseling 2001).

Muscles − Can retain PQ and reduce excretion of PQ (Lee 2008)

Lungs – USEPA (1997) – Chronic inflammation, increased weight, deeper breathing, thickening of alveolar walls, fibrosis, edema and alveolar hemorrhage.

Liver – USEPA (1997) reported cell proliferation and fibrosis of the bile duct in rodents.

Kidneys – USEPA (1997) – Rough surface and renal tube degeneration in rodents.

Adrenals – USEPA (1997) – Cysts in rodents.

Thymus – USEPA (1997) – Atrophy of the thymus gland in rodents.

Cardiac and hematolymphatic system – IPCS (1984) – Damage to the myocardium and hemolytic anemia, myocardial contractile dysfunction (Ge et al. 2010); inhibited synthesis and accelerated breakdown of heme in blood (Noriega et al. 2002); swelling of the spleen and swelling and inflammation of the mesenteric lymph node and leukemia in rodents (USEPA 1997).

Cancer – Weak to no evidence USEPA (1997); IPCS (1984); EC (2002); and FAO 2008). Many epidemiological studies have associated PQ with skin cancers in humans, including squamous cell carcinoma associated with combined sunlight exposure and bypridilium precursors among workers in PQ factories in Taiwan (Jee et al. 1995). Skin cancers have been reported on applicators after exposure to PQ in coffee and banana growing regions of Costa Rica (Wesseling et al. 1999; 1996). Skin cancer occurred on PQ applicators who wore clothes soaked with PQ (Anderson and Scerri 2003) and an increased risk of childhood leukemia was suggested if pregnant mothers were exposed to PQ during the second trimester (Monge 2007). Several studies have shown weak to no evidence of possible links with PQ and non-Hodgkins lymphoma (Park et al. 2009), brain cancer (Lee et al. 2005), and breast cancer (Engel et al. 2005).

Genotoxicity and mutagenicity – EC (2003) and IPCS (1984) concluded PQ was not genotoxic in *in vivo* studies but was in some *in vitro* studies. The FAO (2008) concluded PQ was mutagenic in human lymphocytes and Chinese Hamster lung fibroblasts but not in rat liver cells and mouse lymphocytes. The CA EPA (1993) concluded there was evidence of PQ causing genotoxicty. Several scientific papers relate PQ exposure to genotoxicity including rat bone marrow (D'Souza et al. 2005; Black et al. 2008); Chinese toad (*Bufo gargarizans*) (Yin et al. 2008) and cytotoxic and genotoxic effects in goats and human lymphocytes (Jovtechv et al.), mutations in skin of mice (Van Osch et al. 2010), and a teratogen effect in frogs (Osano et al. 2002).

Endocrine disruption – Not assessed by regulatory agencies; but in studies on animals, PQ decreased testosterone and the follicle stimulating hormone (Zain 2007); testosterone decreased in frogs (Quassinti et al. 2007); and detectable PQ levels have been detected in thyroid glands of victims of poisoning (Goldver et al. 2010).

Reproduction – The USEPA 1997; EC 2003; and FAO 2008 say PQ has no specific effects on reproduction. The USEPA (1997) reported necrosis and atrophy of the testes, ovaries, and uterine cysts and polyps with

chronic exposure. Wesseling et al. (2001) reported animal studies show no reproductive effects at PQ doses below the maternal toxic dose. High doses of PQ caused fetal mortality in rats and increased the percentage of abnormal eggs in hens (Extronet 1996). These results suggest PQ does not cause reproductive problems at normal exposure doses. Other researchers have shown PQ at 8μM reduced development of mouse embryos (Hausberg et al. 2005), injured mouse stem cells at PQ concentrations 800-fold less than concentrations that injured mouse stem cells (Perla et al. 2008), and impaired development of mice brains (Palacios-Pru 2005). Zain (2007) concluded that PQ is toxic to male reproductive function both by oral and dermal routes in rats, although these studies were conducted at extremely high PQ concentrations of 5 and 20 mg/kg of body weight. PQ has been shown to cross the placenta in mothers' blood (Tsatskis et al. 1996) and Wesseling et al. (2001) reported fetal death in pregnant women exposed to PQ.

Birth defects – There is considerable controversy related to any PQ effects on birth defects as regulatory agencies say there is no effect, but independent studies indicate birth defects can occur after exposure. High dose exposure studies show PQ effects on fetal body weight and delayed ossification of various body regions for bone development, but data does not support normal exposure being a problem in causing birth defects (USEPA 1997). Vismara et al. (2000; 2001a; 2001b) and Osano et al. (2002) showed PQ had embryogenic and teratogenic activity against frog as well as growth retardation of tadpoles.

Nervous system – Neurotoxicity is not studied by regulatory agencies, so PQ is not considered to be a neurotoxin. However, animal studies have demonstrated a possible link (IPCS 1984) and recent studies with laboratory animals show PQ induced reduction in neurotransmitters in the brain (Endo et al. 1998; Miranda-Contreras et al. 2005) and reduced motor activity of test animals (Chanyachukul et al. 2004; Muller-Ribeiro et al. 2010; Songin et al. 2010) and induced anxiety (Littlejohn et al. 2008). Other researchers have shown PQ exposure killed brain neurons (Stelmashook et al. 2007), causing damage to the hippocampus that affects learning and memory (Chen et al. 2010). Interactions between thermal stress and PQ resulted in damage to spinal neurons (Kriscenski-Perry et al. 2002). The CAEPA (2010) concluded PQ is a neurotoxin impacting brain function based on direct evidence that PQ can penetrate the central nervous system.

Immune system – Little research has been conducted on PQ and any effects on the immune system. A few studies have shown PQ can negatively affect the immune system. Rapetto and Baliga (1996) showed PQ exposure in frogs decreased macrophages, increased the release of histamine from mast cells in rats (Sato et al. 1998) and caused inflammation of umbilical cells (Yu and Nie 2010) and at high doses suppressed cellular and humoral activity in rats (Riahi et al. 2010)

Cases of PQ oral ingestion resulting in death

Since the introduction of PQ in 1963, it has been implicated as a causal agent in human deaths including intentional ingestion for suicides (Castro-Gutierrez et al. 1997) and accidental ingestion (Castro-Gutierrez et al. 1997). PQ is toxic if ingested at 10 mg/kg body weight (Sabzghahaee et al. 2010; Proudfoot et al. 1979). In the developing world it has been estimated (Gunnell 2007) that up to 1/3 of all suicides result from pesticide ingestion and PQ has often been involved. Other reports showed PQ suicides accounted for ~232 deaths worldwide between 1962 to 1974 (Taylor et al. 1985) and PQ is the preferred choice for suicides in Asia and the Pacific Islands (Naito and Yamashita 1987; Taylor et al. 1985; Perriens et al. 1989). In Costa Rica, PQ caused more deaths than any other pesticide including 86% of all deaths from occupational pesticide poisonings (Wesseling et al. 1993). Even when a person survives PQ poisoning, they suffer fibrosis and pulmonary function abnormalities, especially decreased diffusing capacity (Anderson 1970; Fisher et al. 1971; Fock 1987; Hettiarachchi and Fernando 1988)

Accidental ingestion is less frequent but is still a concern in the developing world where PQ is often repackaged or stored in used soda drink containers and not properly labeled (Wesseling et al, 1993; 1997), increasing the potential for accidental ingestion to occur.

Parkinson's disease

Numerous scientific articles have conducted research on possible links of PQ exposure and the onset of Parkinson's disease in humans. These studies include both laboratory experiments with test animals exposed to various doses of PQ and subsequent effects on important compounds in the body associated with the onset of Parkinson's disease and epidemiology studies conducted with human populations having known exposure to PQ for associations with higher occurrence of Parkinson's disease in such populations. The USEPA (2016) stated: "There is a large amount of epidemiological data on the association of PQ with Parkinson's disease and connections to thyroid disease, wheezing, and chronic bronchitis in non-smoking women". However, the USEPA says additional research is necessary to show a more direct effect.

Research on PQ and its health effects on humans, especially that associated with Parkinson's disease and epidemiology studies on danger of exposure, are controversial. Most researchers involved in laboratory test animal studies conclude that PQ exposure can result in negative effects (lack of production) in the regions of the brain that produce dopamine (the important human hormone in non-Parkinson's disease humans). The major question surrounding all this research is whether PQ, if it enters the body, could cross the blood brain barrier that excludes toxic chemicals from entering the brain, resulting in a negative effect. Researchers in the past thought that PQ could not cross this brain barrier (Cook et al. 2016), although, recent papers show PQ can cross the blood brain barrier by use of a carrier mediated process using a neutral amino acid transporter (Shimizu et al. 2001; Ogawa et al. 2001, McCormick et al.; Costa et al. 2008).

Parkinson's disease is a progressive neurological disease in humans characterized by selective degeneration and death of dopaminergic neurons in the pars compacta of the *Substantia nigra* (SNpc) in the human mid-brain. This process leads to aggregation and deposition of specific proteins (α synucleins), oxidative stress, and mitochondrial and protosomal dysfunction and accumulation of ubiquitin proteins causing defects in cellular trafficking and apoptosis (cell death). Another characteristic is the presence of proteinaceous inclusions (Lewy Bodies (LB) in the brain. Parkinson's disease is characterized by loss of dopamine secreting neurons from the mid-brain and is characterized by slowness of movement (bradykinesis), rigidity, motor deficits, postural instability, and tremors (Abeliovich 2007; Abeliovich and Gitler 2016; Vaccari et al. 2017). The specific cause(s) of Parkinson's disease are elusive but it has been suggested there is multifactorial pathogenesis involving genetic factors (genetic predisposition), aging, and possible exposure to certain environmental chemicals including pesticides (Abeliovich 2007; Di Monte et al. 2003; Warner and Shcapira 2003, Goldman 2012; Abeliovich and Gitler 2016; Vaccari et al. 2017).

Difficulties exist in determining specific causes and the onset of Parkinson's disease as no animal models used in Parkinson's disease research accurately replicate the spectrum of disease features at the organ or cellular levels. Epidemiological evidence suggests both environmental and genetic factors interact for disease occurrence. Such interactions add to the complexity of making determinations of a specific cause and effect or the importance of any single disease inducing factor in Parkinson's disease (Abeliovich 2007). The definitive answer to whether PQ exposure can result in Parkinson's disease is still unclear and the controversy will continue. Several papers are described below on research showing both an association and no association between exposure to PQ and eventual Parkinson's disease development in laboratory experiments with model animal systems and from human epidemiological studies.

In the PQ paper by Watts (2011) and a similar paper by Isenring (2017) the authors cite over 100 papers that implicate PQ with Parkinson's disease from both laboratory and epidemiology studies and the reader is referred to these papers for further study.

Research on PQ and Parkinson's disease

There has been much discussion and research regarding possible negative effects of exposure to certain pesticides and a subsequent increased potential for Parkinson's disease occurrence in humans. The types of chemicals implicated are those that share the ability to cause oxidative stress (PQ is an oxidative stress chemical) which is considered to be a key factor in pathogenesis of Parkinson's disease (Dretchsel and Patel 2008; Allen and Levy 2013, review). These chemicals can also cause mitochondrial dysfunction, α synuclein fibrillation, decreased dopamine level and subsequent neuronal cell loss caused by apoptosis and autophagy, an inhibition of ubiquinone and proteasome systems, and the induction of synucleinopathy and tauopathy (Baltazar 2014; Dinis-Oliveira et al. 2009; Drechsel and Patel 2008, Abeliovich 2010). All these effects can cascade to result in the degradation of dopamine neurons in the *Substantia nigra* of the human brain, which is the key aspect of Parkinson's disease in humans (Mostafalalou and Adddollah 2013).

Several papers provide summaries of present information on PQ, its use, effectiveness and potential, or lack of effect on human health (Watts 2011; Brown et al 2004; Isenring 2017). The papers by the Pesticide Action Network (Watts 2011 and Dinham 2004) argue that PQ should be banned because its negative health effects on humans are unacceptable. These papers contain over 300 referenced research papers showing links between PQ and human health problems. Papers by Brown et al. (2004), Brooks et al. (1999), and Cook et al. (2007) argue that PQ is safe when used properly and so it poses no unacceptable health risks to humans. The question posed by the editor of Outlooks on Pest Management in 2004 (Coppling 2004) is "Who is Right?", and this is the question that all regulatory agencies must address in determining whether PQ is an acceptable herbicide for use in agriculture and poses no unacceptable risks.

Evidence both of a PQ effect and of no PQ effect on Parkinson's disease has been demonstrated in several laboratory studies with animals, mainly mice. Experiments have shown mice have reduced motor function and a dose dependent loss of striatal tyrosine hydroxylase (TH) fibers and SNc neurons after exposure to PQ (Brooks et al. 1999; McCormack et al. 2001; Li and Sun 1999; 2002; Rappold et al. 2011). Others argue PQ may be useful in laboratory studies because of its presumed ability to induce lipid bodies (LB) in DA neurons (Manning-Bog et al. 2002) but Miller (2007) says laboratory results are contradictory with variable cell death and effects on striatal DA content. Research in a 13-week feeding study on mice where PQ was fed at 0, 10 and 50 ppm in the diet once per week caused no effect on striatal dopamine or DP metabolite concentration in mice brains (Minnema et al. 2013). These authors said that other PQ studies that showed an effect related to Parkinson's disease used PQ administered via the intraperitoneal route (Brooks et al. 1999; Gollamudi et al. 2012; Peng et al. 2004; Jiao et al. 2012; McCormack et al. 2002; Yin et al. 2011), which is unrealistic compared to any typical route of PQ entry into the body. These authors' argument against the PQ effect in animal studies is that the animal system models used do not represent the human exposure level or appropriate conditions for a response. Another argument is that the strain of mice used in PQ and Parkinson's disease studies, C57BL/6, is particularly sensitive to MPTP, a known chemical that causes Parkinson's disease symptoms in humans. Further, the IP dose used in many studies showing a PQ effect is 1/3 the known lethal PQ dose when injected at 10 mg/kg body weight once a week over a three-week period. Their arguments are further supported by research of Breckenridge et al. (2013) who duplicated test conditions previously used to show a relationship of PQ to Parkinson's disease and an interlay study by Smeyne et al. (2016) where PQ was administered at the maximum tolerable concentration and in neither study, could the researchers show any PQ effect on neuropathology associated with Parkinson's disease. Lock and Wilks (2001) argue that the methods used to expose mice to PQ by the intraperitoneal route do not reflect typical human exposure (oral, dermal, or inhalation) in normal agriculture use practices as the majority of exposure studies have shown the greatest operator exposure is to their skin. The greatest potential for exposure exists when PQ is mixed and applied by knapsack, tractor, or airplane. Further, mice skin absorption of PQ is twice as high as human skin. This makes it difficult to interpret the relevance of such studies to actual human response, especially since

the exact mechanisms involved in Parkinson's disease is still unknown. These arguments do not discuss other studies showing that dermal exposure to humans can lead to serious health problems and some have been related in epidemiology studies to Parkinson's onset.

Recent medical research on Parkinson's disease and PQ by Reczek et al. (2017) identified three genes in humans that may lead to Parkinson's disease after exposure to PQ. Humans with high levels of these genes could be more susceptible to PQ poisoning when working with the herbicide and potentially more susceptible to Parkinson's disease onset. Guangwei et al. (2014) evaluated changes to the *Substantia nigra* (SN) function in brains of subjects who had high levels of pesticide exposure and those with no exposure and those with Parkinson's disease. Magnetic resonance imaging (MRI) and diffusion tensor (DTI) images of patients for DTI measures in the SN, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), and Parkinson's disease patients showed the expected significant changes in all DTI measurements in the SN. The pesticide-exposed subjects, compared to the controls, had significantly lower FA values and the control had no change. This study demonstrated that microstructural changes in the SN of human subjects with chronic pesticide exposure may mark "one of the hits" leading to Parkinson's disease that underlie the increased risk of Parkinson's disease in pesticide users found in epidemiological studies. Jones et al. (2014) reviewed technical and biological mechanisms that contribute to inconsistencies regarding PQ neurotoxicity and hypothesized that individual genetic variations in susceptibility generate major differences in neurotoxic risk and functional outcome for humans exposed to PQ.

Epidemiological evidence of PQ involvement in Parkinson's disease

Hill (1965) was one of the first scientists to suggest an association between the environment and disease occurrence and later, by Seidler et al. (1996) and for environmental factors including pesticide exposure, rural living, farming, and onset of Parkinson's disease (Warner and Schapira (2003). There has been considerable epidemiological research conducted that demonstrates an association of human exposure to pesticides (Dick et al. 2007; Le Couteur et al. 1999; Li et al. 2005; Priyadarshi et al. 2000; Priyadarshi et al. 2001; Vander Mark et al. 2011; Freire and Koifman 2012; Semehuk et al. 1992; Seidler et al. 1996), specifically to PQ (Hartzman et al. 1990; Li et al. 2005; Brown et al. 2006; Van Maele-Fabry 2013; Pezzoli and Cereda 2013; Ntzani et al. 2013) that leads to a higher risk for development of Parkinson's disease. Brown et al. (2006) showed a PQ effect on constituent factors of Parkinson's disease such as the DP system and α synuclein aggregation and concluded that the weight of evidence is sufficient to show an association between pesticide exposure and development of Parkinson's disease. However, they further stated that the evidence is inconclusive to deduce that this is a causal relationship or that a specific relationship for any specific pesticide or other exogenous toxicant exists. The multifactor etiology of Parkinson's disease hampers unequivocally establishing the role of any individual contributory causal factor.

These epidemiology studies are often criticized because of differences in design, case, and control selection problems, sample size, lack of satisfactory information about definition, extent and duration of PQ exposure, non-specificity of particular pesticides involved, as well as accurate Parkinson's disease analysis of subjects examined and bias (Berry et al. 2010, Vaccari et al. 2017; Cook et al. 2007). Other researchers have shown no relationship (Breckenridge et al. 2016; Brent and Shaeffer 2010; Bronstein et al. 2009; Mandel et al. 2012) and others suggest it is not possible to assume cause and effect between PQ and Parkinson's disease based on the existing epidemiological research (Adami et al. 2011).

Additional epidemiological studies have been conducted with specific test populations since the late 1990s. The Agriculture Health Study (Alavanja et al. 1996) was an extensive evaluation of pesticides and rural living influences on health; Gray et al. (2000) evaluated this for improved approaches for future studies and Kamel et al. (2006) where pesticide exposure was associated with self-reported onset of Parkinson's disease. The National Institute of Environmental Health Sciences in the US showed in a 2011 study that people

exposed to PQ were twice as likely to develop Parkinson's disease. Other systematic reviews and meta-analysis of epidemiology studies with humans and pesticide exposure were able to detect a positive association with pesticide exposure and Parkinson's disease onset (Priyadarshi et al. 2000; Priyadarshi et al. 2001; Van der Mark et al. 2011; Freire and Koifman 2012; Zhang et al. 2016). Other epidemiology population studies have shown a higher incidence of Parkinson's disease in people exposed to pesticides (Freire and Koifman 2012; Van Maele-Fabry et al. 2012). The meta-study by Van der Mark et al. (2012) reviewed 39-case control studies, four cohort case studies, and 3-cross sectional studies and concluded that exposure to pesticides (insecticides and herbicides) can lead to an augmented risk of Parkinson's disease. One caveat of this study was there was no mention of which specific pesticides caused such an effect.

Several studies of epidemiology and studies that reanalyzed previous epidemiology studies disagree with the conclusion of a strong link between PQ exposure and the incidence of Parkinson's disease development. Studies by Kamel (2007) evaluating results of a 1996 study of farmers exposed to pesticides in North Carolina and Iowa showed an odds ratio of 1.0 for the occurrence of PQ exposure and Parkinson's disease development. Analysis of this research paper by a multidisciplinary group of 29 independent experts on the contribution of different environmental factors to Parkinson's disease (Bronstein et al. 2009) concluded that there was "Inadequate/insufficient evidence to determine whether an association exists" for PQ and the onset of Parkinson's disease.

Tanner et al. (2011) determined whether pesticides that cause mitochondrial dysfunction or oxidative stress are associated with Parkinson's disease on 23 human subjects and the adjusted odds ratio for PQ causing Parkinson's disease were 2.5. However, Mandel et al. (2012) concluded Tanner's study was difficult to interpret due to important methodological issues and that the results were questionable. Mandel et al. (2012) provided a critical review of other epidemiological studies investigating any association between PQ and Parkinson's disease onset and suggested that many studies are characterized by weaknesses in their design, particularly the assessment of past participant exposure, and as such, provide an inconsistent picture of whether PQ is involved.

Breckenridge et al. (2016) evaluated 20 published epidemiological studies on PQ and its potential to induce Parkinson's disease and determined that in only two of the twenty studies was there both individual reporting of whether participants were exposed to PQ and medical confirmation of diagnosis of Parkinson's disease confirmed by examination by a medical expert. In these studies (Firestone 2005; 2010), the association between exposure to PQ and the diagnosis of Parkinson's disease was not statistically significant. Recently, Firestone (2010) reported that this cohort of subjects had a relative risk ratio for Parkinson's disease development near unity with unexposed subjects.

Tomenson and Campbell (2011) concluded that there was no evidence of an increased incidence of Parkinson's disease among PQ production workers based on mentions of Parkinson's disease on the death certificates of workers. The argued strength of this study was suggested to be related to a likely higher exposure (level and duration) of workers engaged in PQ production during the 1960s, 1970s, and 1980s than many of the human subjects in case-control studies classified as exposed to PQ. However, this opinion assumes that all humans who use PQ in both mixing and applying follow all safety regulations as stated on product labels and wear protective clothing and other personal safety equipment to minimize their exposure. This is often questionable in developing country agriculture and where repeated applications are made within and over years and exposure can be extreme.

Brent and Schaeffer (2011) assessed whether confirmed high-dose PQ exposure was associated with the development of Parkinson's disease. The researchers did a systematic review of all published cases of PQ toxicity that met a case-definition of PQ poisoning and who either recovered or lived for at least 30 days or for 15 to 30 days, although, those people who died, would not have developed Parkinson's disease in any case.

Cases were included if they contained sufficient information to determine whether the survivors developed signs of Parkinson's disease. This analysis found no connection between high-dose PQ exposure in humans and the development of Parkinson's disease.

Pro and con arguments about PQ and Parkinson's disease associations

Cook et al. (2016) in a letter to the editor of *Laboratory Investigations* argued that research by Zhang et al. (2016) showing the definite effect of PQ exposure on Parkinson's disease epidemiology was inaccurate. Cook offered evidence, with several referenced research papers, that much of the Parkinson's disease laboratory and epidemiology research proposing links of human exposure to PQ and subsequent onset of Parkinson's disease are unrealistic, conducted poorly and did not show a direct cause and effect of PQ exposure and onset of Parkinson's disease. Interestingly, Thompson and Zhang (2016) authors of the paper Cook criticized responded by stating that Cook was mistaken in his views and did not fully understand the analyses Zhang et al. (2016) had conducted. Thompson and Zhang (2016 b) provided insightful arguments. They suggest that much of the epidemiological and laboratory research showing an effect of PQ on Parkinson's disease are useful for learning more about potential links between PQ and Parkinson's disease. They argue the criticisms by Cook et al. (2016) and others (Mandel et al. 2012a and 2012b; Breckenridge et al. 2016; Tomenson and Campbell 2011; Brent and Schaeffer 2011) of laboratory and epidemiological studies were invalid for PQ association with Parkinson's disease and suffered from experimental deficiencies that call into question their results, i.e., no PQ involvement in Parkinson's disease development.

Professor Sir Colin Berry (Emeritus Professor at Queen Mary, University of London and Professor Pierluigi Nicotera (Founding Director of the German Center for Neurodegenerative Diseases, Bonn, Germany) concluded that the evidence available from epidemiological studies was fragmentary and insufficient to establish whether herbicides and, PQ in particular, increase the risk for Parkinson's disease. They further concluded that the overall epidemiological evidence from combined exposure studies and those limited to PQ alone did not support the existence of a specific association between PQ and Parkinson's disease. The analysis was subsequently published (Berry et al. 2010).

Kamel Freya author of the NIEHS (Kamel et al. 2006) study and a noted Parkinson's disease researcher (Kamel et al. 2007) says research evidence of PQ exposure to humans and an effect of increased Parkinson's disease potential is about as persuasive as things get in medical research (Kamel 2013). Dr Samuel M. Goldman, an epidemiologist in the San Francisco Veterans Affairs health system who has published extensively on Parkinson's disease says: "The data is overwhelming" linking PQ and Parkinson's disease (*NY Times* 2011).

Laboratory studies with animals (Watts 2011), show a possible link to PQ exposure and a potential for development of Parkinson's disease. The argument that the mouse line used in Parkinson's disease research, which is highly susceptible to MTPT, a known chemical that can cause Parkinson's disease in humans, should not be used with PQ, counters every typical accepted medical research protocol with animals. Such an argument essentially says that animal research cannot be transferred to a potential similar response of PQ in humans, or to be more specific, do not believe medical research results if they counter your own inherent bias.

Epidemiological case studies are difficult to conduct based on the many problems with human research as discussed by Vaccini (2017) but when done correctly, they can show a cause and effect of chemicals and onset of disease. The evidence provided in the toxicology sections show that PQ can have a serious negative effect on human health after exposure. The evidence shows that PQ is a dangerous herbicide with potential to cause grave danger to spray applicators.

Alternative herbicides to replace PQ if banned

Alternative Treatments. Brown et al. (2004) argue that there are no suitable alternative herbicides for obtaining the effective weed control obtained by PQ. The argument is that there are no broad-spectrum herbicides with the rapid action of PQ or its quick rain fastness. The argument continues that other broad-spectrum herbicides are slower acting in controlling weeds, are strongly or moderately systemic, are sensitive to rainfall and reduced activity after application, are less precise in their use, and do not offer crop safety and soil conservation. The argument that no acceptable alternatives to PQ exist is weak in almost all aspects except the rapid kill.

Alternatives

Glyphosate has broad-spectrum activity, is systemic, kills both annual and perennial weeds and is widely used in no-till, although, complete weed death may require 7−14 days and it is less rainfast.

Glufosinate is a broad-spectrum herbicide, mostly considered a contact herbicide but does translocate in some species, has good rainfastness, and can be used in no-till and many crops where PQ is used and has similar soil inactivation characteristics to PQ (WSSA Herbicide Handbook, 2015).

Other contact herbicides including many members of the **diphenyl ether** herbicide family are effective against broadleaf weeds, have low mobility in soil, and for some members of this class, have short-term soil activity against newly germinating weeds.

The grass-specific herbicides including the **arlyoxyphenoxy-propionate** and **cyclohexanediones** are effective against a variety of annual and perennial grasses and have excellent safety in all broadleaf crops such as cassava. These herbicides cause grass weeds to stop growing almost immediately with death occurring within 7−14 days.

Many broadleaf herbicides considered as growth regulators including the **phenoxy acetic acids (2, 4-D), benzoic acids (dicamba), and pyridines** have activity against most annual and perennial broadleaf weeds, are systemic, have limited soil activity and limited soil mobility, and can be precisely applied in susceptible crops. These, especially the phenoxies and benzoics, are commonly used in no-till site preparation (WSSA Herbicide Handbook, 2015).

Possible Actions by NAFDAC on PQ Use in Nigeria

1. Ban PQ use and sale in Nigeria, as its use is a danger to the health of applicators and others as confirmed in the scientific literature and as outlined in this paper.
2. Allow PQ to remain on the market in Nigeria under present regulations. **This is not recommended**, as the wealth of information regarding negative effects of PQ on humans and potential for short- and long-term negative effects on human health are overwhelmingly strong.

This action would require establishing NAFDAC to establish regulations for the sale and use of PQ and to make PQ a restricted use pesticide (RUP). Regulations similar to those established by the US EPA and information in the US CDC document cited in this paper should be used as a guide to establish such regulations. These regulations would require all pesticide applicators who purchase and use PQ to be trained and licensed. Regulations for handling, application, and disposal of PQ would need to be strictly enforced. Such regulations would result in safer use practices for PQ, but as described in this report, not eliminate the potential negative health effects of PQ use. Regulations once established have to be enforced so unlicenced applicators or persons do not have access to PQ. (US Center for Disease Control)CDC), https://emergency.cdc.gov/agent/PQ/basics/facts.asp) and The US Environmental Protection Agency (USEPA).

3. Determine that PQ is an important herbicide for use in Nigerian agriculture but medical evidence requires that stricter regulations for its sale and use be established to allow its use in a manner that reduces to a minimum the danger to applicators and the public.

We strongly encourage NAFDAC to ban Paraquat sale and use in Nigeria. This is based on the current situation in Nigeria that no mechanism or regulations exist to establish or enforce licensing of applicators or regulations of Paraquat sale and use as a Restricted Use Pesticide.

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