SYNGENTA CROP PROTECTION

BASEL, SWITZERLAND

Paraquat dichloride

REGULATORY STRATEGY

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1. EXECUTIVE SUMMARY

Paraquat continues to attract significant regulatory and NGO scrutiny, often as a result of the perceived environmental persistence or acute toxicity hazard to man. Development of science, particularly in the field of neurotoxicity, and the development of precautionary regulatory policy over risk based decision making, present the prospect of additional challenges in the future. Despite paraquat registrations remaining insecure and hence requiring considerable proactive maintenance, the regulatory "license to sell" situation remains generally under control. The area of increasing difficulty is the "freedom to sell". Retailers and other organisations are increasingly placing paraquat on a negative or black list, based on image, hazard or perceived risks, indicating that growers can not use the product. Together, these developments present a serious threat to Syngenta's Gramoxone business objectives. The key regulatory strategy elements are:

- Defend all registrations
- Consolidate and gain international consensus of the human and environmental safety of paraquat under the current regulatory risk assessment regime
- Provide regulatory support to sustainable agriculture and food industry activities to ensure Syngenta has "Freedom to Sell" paraquat as well as "Licenses to Sell"
- Build capability to defend both the license to sell and freedom to sell paraquat in potential future risk assessment and hazard paradigms
- Prepare the regulatory environment for the most effective introduction of improved formulations from 2004
- With the introduction of improved formulations set a new standard for paraquat products and drive a substantial change in the product image with both regulators and the non-regulatory stakeholders that influence the licenses and freedom to sell paraquat

2. BUSINESS OBJECTIVES/STRATEGY

Paraquat, as the dichloride salt, is a non-selective contact herbicide for total vegetation control in a wide variety of uses, predominantly in terrestrial weed control outlets. Paraquat is one of the world's number two herbicide in sales terms and a "blockbuster" product for Syngenta. The top 10 markets (USA, China, Mexico, Brazil, Japan, Thailand, S. Korea, Malaysia, Indonesia and Australia) account for 70% of the Gramoxone business. Central America accounts for a further 11%. The business objective in 2003 is to achieve global GRAMOXONE sales of ~$420M, rising to $498M in 2006. Maintain sales in developed markets, and to grow sales in developing markets. Growth is driven by 5 rapidly developing markets (China, Thailand, Indonesia, Malaysia and S Korea) through progresion from handweeding and greater adoption of minimum tillage techniques. India also presents potential future growth opportunity. In the mature and developed markets it is critical that registrations and share are held, with Australia being one of the few developed markets set to grow due to paraquats potential as a glyphosate resistance breaker. Major competitive threats in priority are from glyphosate, generic paraquat and glufosinate. The key strategy elements are –

- Vigorously defend all registrations and uses
- Use economies of scale, quality and brand strength to defend molecular share
- Drive out non value adding complexity and cost from the supply chain
- Develop markets and product positioning to achieve "technical share" in key markets and gain new users in developing markets
- Continued investment in Gramoxone to ensure that brand awareness is obtained or sustained to support market share goals
- Proactive communications / targeted collaborations with key influencers to improve product image / raise purchase consideration
- Introduce improved formulations to substantially changing the product image

3. REGULATORY TARGETS

- Achieve 91/414/EEC Annex I listing in the EU by 1Q 2003 without major new restrictions
- Achieve re-registration under the Australian ECRP review without major new restrictions
- Consolidate the international consensus on toxicology via the CCPR/JMPR review in 2003
- Seek a revised FAO specification for high quality paraquat dichloride technical during 2003 and for paraquat formulations to follow.
- Seek de-restriction in Indonesia
- In every country, obtain the most favourable classification and labelling of Gramoxone products, consistent with national legislation and Syngenta's position on product stewardship. Particularly in the EU, as a consequence of the revision of the Dangerous Preparations Directive (DPD)
- To support future business objectives, ensure that paraquat in India progresses from "deemed registration" status to "normal registration" without major new restrictions and that the outcome of the review is consistent with other international reviews

4. CURRENT REGULATORY STATUS

4.1. EU Annex I inclusion

An SCPH decision on Annex I listing is anticipated in Dec 2002 or 1Q'2003. Paraquat was on the first list of existing compounds for review under 91/414/EEC. PSD in the UK is the rapporteur.

4.2. FQPA status

EPA considers the tolerances in the Paraquat Dichloride Re-registration Eligibility Document (RED) to be reassessed to FQPA requirements. EPA has determined that there is a reasonable certainty that no harm will result to infants and children or to the general population from aggregate exposure to paraquat dichloride residues. EPA does not believe that the effects produced by paraquat would be cumulative with those of other structurally related compounds.

4.3. Regulatory status

Paraquat is among the most widely registered pesticides in the world. It is registered and/or sold in over 120 countries including all the major agricultural markets and those with the most demanding regulatory systems (See appendix 2). Registrations have been subject to review in many territories as a result of routine national re-registration processes or special reviews triggered by public pressure and/or specific regulatory concerns. Paraquat is not registered in certain territories. In a significantly greater number of territories world-wide paraquat products are subject to regulatory restrictions, often as a result of the perceived acute toxicity hazard to man. Key regulatory data (ADI, AOEL) are provided in appendix 1.

Paraquat has been reviewed under FQPA in the USA and is currently under review within the EU. Paraquat is also undergoing a major regulatory review in Australia and the Existing Chemicals Review Programme (ECRP). Paraquat has been reviewed by the World Health Organisation (WHO) with the United Nations Environment Programme (UNEP) in 1983, and by the International Programme on Chemical Safety in 1991 resulting in the publication of the Environmental Health Criteria 39 and the IPCS Health & Safety Guide No 51, respectively. Paraquat was reviewed by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) in 1986 and is subject to a periodic reevaluation in 2003.

5. CLASSIFICATION AND LABELLING

Under the WHO scheme paraquat and Gramoxone are classified as moderately hazardous (class II), a yellow band product. The WHO classification is based on acute oral toxicity. Paraquat is of low toxicity by the dermal route, is a slight skin irritant and a moderate eye irritant. Gramoxone is moderately toxic by the dermal route, is a moderate to severe skin irritant and is moderate eye irritant. Paraquat is extremely toxic by inhalation but the size of spray particles used in agricultural practice are way beyond the respirable range and so inhalation toxicity is not considered to be a toxicological endpoint of concern for Gramoxone. EU 1999/45/EC (DPD) hazard classifications are 'Very Toxic by inhalation', 'Danger of serious damage to health by prolonged exposure', 'Very toxic to aquatic life', 'Dangerous to the environment'.

In some territories Gramoxone is excessively labelled as if in WHO red band. This is often a consequence of an internal policy for labelling Gramoxone, introduced in the early 1970's, in response to the early fatal drinking accidents. This required labels to carry a "skull-and-crossbones" symbol. Later it was recognised that this may attract the potential suicide population and so contribute to notoriety. In 1995 the previous global labelling policy was revoke in favour of Gramoxone being subject to the national classification schemes or where these did not exist the WHO scheme.

6. MANUFACTURING

Syngenta manufacture paraquat using two high quality processes. The Low Temperature Sodium (LTS) process is operated in Bayport USA and the ammonium cyanide process is operated in Huddersfield UK and Nantong China. The main global formulation facility is now Seneffe Belgium. Supply chain initatives are ongoing to maximise flexibility and further reduce complexity, now and as consequence of the introduction of the improved formulations from 2004.

7. REGULATORY ISSUES AND MANAGEMENT TACTICS

7.1. NGOs

Paraquat has long been targeted by certain NGOs as a compound to be banned or severely restricted. NGOs typically focused on the emotive response as a result of numbers of human fatalities rather than on the circumstances in which they occurred. In more recent publications and campaigns, the focus appears to have switched to include accidental and occupational injuries in circumstances of poor practice in developing countries; environmental issues; neurotoxicity and cumulative effects of pesticides. The current image of paraquat (held and promoted by NGOs) represents a very serious threat to Syngenta's paraquat business objectives. The proposed strategy is to

- selectively adopt a proactive and direct approach with certain NGOs considered to have common ground with Syngenta in the area of sustainable agriculture

- adopt a reactive/indirect approach with other NGOs philosophically opposed to paraquat.

The timing of pusuit of this strategy needs to avoid wider and protracted discussion at this critical phase of the EU review. The introduction of improved formulations employing the prometheus technology from 2004 is considered the optimum platform for embarking on the NGO strategy.

7.2. Acute toxicity to man

Paraquat is moderately toxic by the oral route, but of higher acute toxicity than most herbicides. As with all chemicals, mis-use of 'Gramoxone' can present risks. By far the greatest exposure of users to herbicides is skin contact. Paraquat is not readily absorbed through intact skin and it is not accumulated in the body. However, studies in developing countries under prevailing conditions of use have highlighted a small incidence (typically in around 1% of populations exposed annually) of reversible topical irritation and local symptoms such as nail damage, nose bleeds, skin and eye irritancy. 'Gramoxone' could potentially pose a risk if accidentally consumed. Suicide with pesticides is a significant public health issue in some developing countries. The proposed strategy is -

- to implement the company standard for the minimum recommended spray dilution for 20% bipyridyl-containing formulations when used in knapsack and hand-held sprayers (1:100)
- to support extensive stewardship programmes in developed and developing countries, teaching farmers and their families how to handle agricultural chemicals safely with particular emphasis on the measures that will preclude topical irritation and local symptoms
- to ensure Syngenta meet the FAO specification that stipulates all paraquat product must include a dye and an effective emetic and may contain a stench or thickening agent
- to discourage decanting, offer a range of pack sizes and closed transfer systems so that the product purchased is as close to the quantity needed, delivered with the minimum amount of rehandling
- to actively support projects run by internationally renowned experts and non-governmental organisations working in the field of suicide prevention
- to develop and introduce globally improved formulations employing the prometheus technology designed to impart a significant reduction in oral toxicity harzard and be less topically irritating

7.3. Prometheus project

The Prometheus project is considered a unique opportunity to improve key internal and external stakeholder perceptions and rejuvenate the brand image of Gramoxone. The strategy is

- wherever technically possible paraquat products should employ the Prometheus technology that delivers reduced oral toxicity hazard via the combination of a pH triggered gel, boosted emetic and purgative; an improved topical irritation profile; and enhanced user acceptability via an alternative stench/alerting agent
- The formulations will have new IP and provide a supplychain opportunity to review all formulations and streamline the product range. The regulatory challenge is to achieve the earliest approvals globally, that provide the best platform to realise the many potential competitive advantages and opportunities. This is now the subject of detailed internal discussions with regions and countries. The project remains highly confidential and there remains a general embargo on discussion of the project with any external stakeholders, particularly at this critical time in the EU review. Key elements of the regulatory strategy :
- meet the regulator shortly before the regulatory submission to explain the product benefits, manage expectations and seek fast-track review and or pragmatism over certain study requirement
- post registration seek to gain legitimate competitive advantage by establishing this product as the new minimum standard for paraquat products

7.4. Neurotoxicity

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

- to monitor publications and presentations
- to develop links with key researchers to gain visibility and influence on further work
- to develop capability for Syngenta to repeat and confirm or challenge key findings
- to develop and start proactive implementation of an influencing strategy to ensure
  - that a rational risk assessment will prevail

- to contain any potential impact on Gramoxone
- in the period prior to potential launch of a new product range from 2004, seek to shift the focus of serious PD research to other environmental factors with an exposure profile more consistent with being a PD risk factor.

- to consider appropriate timing for generation of paraquat neurotoxicity studies

7.5. Environmental persistence

The degradation of paraquat is slow. However, paraquat is highly biodegradable and in the unbound state is rapidly degraded, ultimately to carbon dioxide, by commonly occurring soil micro-organisms. Paraquat rapidly binds to soil and is thereby very rapidly biologically deactivated. Paraquat is not unusual amongst pesticides in forming strongly adsorbed residues, which are subsequently slowly degraded in soil. What is different is that there is a method for the extraction of the adsorbed (bound) residue. Paraquat is considered to confer unique benefits for soil health that will continue to be of importance for sustainable agriculture. The strategy is to -

- Emphasise exhaustive long-term field studies demonstrating the lack of consequences (soil-dwelling organisms, leaching, effects on rotational crops, residues in following crops, etc.)
- Strengthen the data in support of rapid biodegradation of available residues
- Seek evidence for & recognition of the positive environmental benefits Gramoxone can confer
- Develop an influencing strategy to question the perception of Gramoxone as being highly environmentally persistent, by focussing on the rapid degradation of biologically available paraquat and the comparison of adsorbed paraquat with conventional "bound residue"
- Support the regulatory position through selective publication in reputable scientific journals and through conduct of work by independent laboratories
- Seek to establish regulatory precedents with diquat, which does not attract the same level of negative emotions as paraquat.

7.6. Regulatory policy

Regulatory policy continues to be developed, increasingly at international and regional levels as well as nationally. This poses a threat to the current regulatory positions achieved for paraquat. Under the prevailing risk assessment paradigm in most countries, anticipated developments include wider adoption of aggregate risk assessment and cumulative risk assessment of materials with common mechanism of toxicity. Under the hazard based precautionary paradigm currently receiving support in the EU, anticipated developments include increased emphasis on comparative assessment potentially including application of the substitution principle. This could involve replacement of higher hazard products with lower hazard products regardless of whether the replaced products have been shown to pose an acceptable risk. The precautionary principle may also be applied to regulatory decisions on issues of current scientific uncertainty; these include cumulative effects of products with different mechanisms of toxicity, and emotional issues such as PD and suicide. The strategy is to –

- Lead national, regional and global industry initiatives to influence regulatory policy development
- Recognise that paraquat registrations remain insecure, and proactively maintain contacts with key national decision makers and influencers to gain early visibility of potential issues and threats, and early opportunities to address them
- Develop and proactively implement dietary exposure and water strategies for paraquat to better demonstrate not only the regulatory standard that "there is a reasonable certainty that no harm will result to the general population, and to infants and children from aggregate exposure to paraquat residues" is met but that there is negligible consumer exposure to paraquat residues.
- Seek local independent support for the record of safety to users, the environment and wildlife, the need for non-selective weed control, and the benefits which give paraquat a unique and continuing important role in sustainable agriculture

7.7. Non-regulatory specifiers

Retailer and other organisations are increasingly placing paraquat on a negative or black list, indicating that growers can not use the product. This represents a very serious threat to Syngenta's ability to sustain registrations in the mid-term. In some cases paraquat is specifically targeted with no objective criteria for exclusion, in others the criteria may inenquitably exclude all 'Toxic' herbicides. Within the EU the Commission already provides subsidies for farmers adopting IPM practices through Directive 2078, this process is likely to accelerate through the reform of the Common Agricultural Policy (CAP). Potential paraquat weaknesses relate principally to classification on the basis of hazard. Paraquat's negative image is a strong 'sustainer', not readily overcome by rational argument. There is clearly a significant short term commercial impact, already apparent in LATAM and certain EU markets. However the exclusion of paraquat from outlets in which it has previously been the product of choice undermines user support for the product ('benefits case') and hence our continued ability to sustain registrations. This is particularly relevant in the case of institutional plantation users, whose loss of support may seriously impact regulatory

defence. The food industry is a much softer target for NGOs than a direct approach to regulators. The food industry is much more vulnerable to public opinion and the effect on its brands, it does not wish to be associated with products having a negative public perception. The strategy is to -

- Seek to improve classification and labelling and the image of paraquat held by key NGO's and food chain stakeholders
- Position Syngenta as a partner in the training and stewardship of its products with selected Food Industry partners
- Seek to influence the development of SA/food chain protocol schemes
- Support development of an improved toxicity product

8. FORMULATIONS

The lead "Gramoxone" formulation is a straight product typically containing 20% paraquat ion, numerous variants exist. Higher strength products are sold in the US and Australia. Various pre-mixes (e.g. with diquat or diuron) are also sold in some markets. Lower strength products are sold in Japan, Germany and France for historical regulatory reasons. The development of the prometheus technology provides an opportunity to rationalise the future product range.

9. GENERICS

Syngenta is the major paraquat manufacturer but Chinese generics exists and are expanding to supply both domestic and export markets. Most currently manufacture via the banned HTS process, quality is poor and product typically does not contain dye, stench and emetic. Quality and process improvement is anticipated. A revised FAO specification under the new process is expected to facilitate better government substantial similarity assessment and enforcement.

10. COMPETITORS

The global Non Selective Herbicide market (including HTC, excluding H&G) was estimated to be worth $3.2bn in 2001. Glyphosate accounts for 80%, paraquat 15% and glufosinate 5%. Monstanto are the biggest and most formidable competitor. A key factor in maintaining paraquat registrations is the agronomic benefits case and the lack of an alternative non-selective contact herbicide with a regulatory profile, which is perceived as 'safer'. The development and registration of such a product would place paraquat registrations at significantly greater risk. This remains a research target for many competitors but no significant new product has been developed for many years. PPGO inhibitor chemistry is a possible threat.

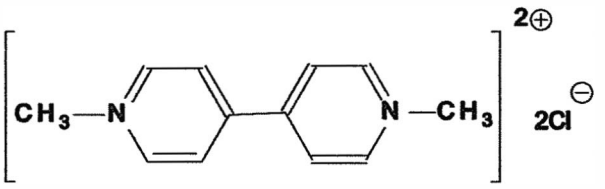
11. LONG-TERM REGISTRABILITY

Paraquat is frequently under threat of severe regulatory restrictions or de-registration due to its high profile, 'bad image'/notoriety and the activities of NGOs. Nevertheless, the current GRA view on registrability over the next five years is that registrations will be maintained in the key global markets in the period 2002 - 2007. Sustaining paraquat registrations has been and will continue to be very demanding of Syngenta regulatory resources. A key factor in maintaining product registrations is the agronomic benefits case and the lack of an alternative non-selective contact herbicide with a regulatory profile which is perceived as 'safer'. The development and registration of such a product would place registrations at significantly greater risk. Increasing emphasis on hazard-based labelling and secondary freedom to sell hurdles based on hazard or image have the potential to seriously undermine the Syngenta paraquat business objectives.

12. MEMBERS OF THE RDT

- Ian Wheals, GRA manager
- ?, EAME regulatory
- Jerry Wells, NAFTA regulatory
- Greg Watson, NAFTA regulatory
- Karla Pires, LATAM regulatory
- Luc Streit, APAC regulatory
- David Vitolo, technical manager
- Mike Clapp, HAES health assessment
- Jeremy Dyson, HAES environmental exposure
- Jim Markle, HAES dietary safety
- Peter Sutton, HAES ecological sciences
- Andreas Stehli, development project leader
- David Scott, stewardship manager
- Martin Wilks, products medical advisor

APPENDIX 1: KEY REGULATORY DATA (ADI, AOEL)

ISO-accepted Common name :	Paraquat, Paraquat dichloride
IUPAC :	1,1'-dimethyl-4,4'-bipyridylium dichloride
CA :	1,1'-dimethyl-4,4'-bipyridinium dichloride (8 & 9 Cl)
Development code:	PP148
CAS No :	4685-14-7 (paraquat)
	1910-42-5 (paraquat dichloride)
EEC No:	225-141-7 (paraquat)
	217-615-7 (paraquat dichloride)
CIPAC No:	56 (paraquat)
Molecular formula:	$C_{12}H_{14}N_2$ (paraquat)
	$C_{12}H_{14}Cl_2N_2$ (paraquat dichloride)
Structural formula:	
Molecular mass:	186.3 (paraquat)
	257.2 (paraquat dichloride)
Melting point :	not measurable decomposes at approximately 340°C
Vapour Pressure:	$<10^{-8}$ k Pa at 25°C
Volatility (Henry's constant):	$<4x10^{-9}$ Pa m^3 mol^{-1}
Appearance:	Paraquat dichloride technical (an aqueous concentrate containing >362g paraquat/l) is a clear dark red-brown liquid with an earthy odour. Pure paraquat dichloride is an off-white hygroscopic solid with no odour.
Solubility in water:	620 g l^{-1} at 20°C
Solubility in organic solvents:	Paraquat is slightly soluble in alcohol (methanol 143gl^{-1}) and practically insoluble in organic solvents (acetone, dichloromethane, toluene, ethyl acetate, hexane <0.1gl^{-1})
Kow:	-4.5 at 20°C
Stability:	Paraquat is hydrolytically and photolytically stable
pKa:	Not measurable
Acute oral MLD (paraquat dichloride):	157 mg/kg and 129 mg/kg to male and female rats
Acute oral MLD (paraquat ion):	113.5 mg/kg and 93.4 mg/kg to male and female rats
Acute oral MLD (Gramoxone):	707 mg/kg and 612 mg/kg to male and female rats
Acute dermal MLD (paraquat dichloride):	>911 mg/kg to male and female rats
Acute dermal MLD (paraquat ion):	>660 mg/kg to male and female rats
Acute dermal MLD (Gramoxone):	590 mg/kg and 735 mg/kg to male and female rats
Acute Reference Dose:	0.0125 mg paraquat ion/kg bw/day (EPA, general population)
	0.0042 mg paraquat ion/kg bw/day (EPA, females 13-50 years)
ADI:	0.005 mg paraquat ion/kg bw/day (Syngenta)
	0.0045 mg paraquat ion/kg bw/day (EPA)
	0.004 mg paraquat ion/kg bw/day (WHO, EU proposed)
AOEL (short-term):	0.0005 mg paraquat ion/kg bw/day (EU proposed)
AOEL (long-term):	0.0004 mg paraquat ion/kg bw/day (EU proposed)
Drinking water MAC:	15ug/l (Syngneta)
	13ug/l (EU proposed)
Carcinogenicity classification:	Group E chemical, one showing evidence of non-carcinogenicity for humans (EPA)
WHO hazard classification:	Class II, moderately hazardous

APPENDIX 2: LIST OF REGISTRATIONS

Paraquat is an agricultural herbicide and is among the most widely registered pesticides in the world. It is registered and/or sold in over 120 countries including all the major agricultural markets with the most demanding regulatory systems such as Canada, Australia, USA, Japan, UK, France, Germany and the Netherlands. (See Table below for complete listing)

Albania	Guyana	Sao Tome & Principe
Algeria	Haiti	St Kitts & Nevis
Angola	Honduras	St Lucia
Antigua & Barbuda	India	St Vincent & the Grenadines
Argentina	Indonesia	Samoa
Australia	Iran	Senegal
Bahamas	Iraq	Sierra Leone
Bahrain	Ireland	Singapore
Bangladesh	Israel	Slovakia
Barbados	Italy	Somalia
Belgium	Jamaica	South Africa
Belize	Japan	South Korea
Bolivia	Jordan	Spain
Botswana	Kenya	Sri Lanka
Brazil	Lebanon	Sudan
Burkina Faso	Liberia	Suriname
Burundi	Macedonia	Swaziland
Cameroon	Madagascar	Taiwan
Canada	Malawi	Thailand
Cape Verde	Malaysia	Trinidad & Tobago
Chad	Mali	Turkey
Chile	Malta	Uganda
China	Mauritania	United Kingdom
Colombia	Mauritius	USA
Costa Rica	Mexico	Uruguay
Cote d'Ivoire	Morocco	Venezuela
Croatia	Mozambique	Vietnam
Cuba	Myanmar	Yemen
Czech Republic	Namibia	Yugoslavia
Dominica	Netherlands	Zambia
Dominican Republic	New Zealand	Zimbabwe
Ecuador	Nicaragua	
El Salvador	Niger	
Ethiopia	Nigeria	
Fiji	Oman	
France	Pakistan	
Gabon	Panama	
Gambia	Papua New Guinea	
Germany	Paraguay	
Ghana	Peru	
Greece	Philippines	
Grenada	Poland	
Guatemala	Portugal	
Guinea	Romania	
Guinea-Bissau	Rwanda	