A3879FA

Paraquat 200 g/L SL

DOCUMENT M-III, Section 3

TOXICOLOGICAL STUDIES

Table of Contents

IIIA 7 TOXICOLOGICAL STUDIES

A3879FA is a soluble liquid (SL) formulation containing 200 g/l paraquat ion as paraquat dichloride. The active ingredient is paraquat ion and all use rates and toxicological endpoints used in risk assessments are quoted as paraquat ion. The product is a contact (post-emergence of the weeds), broad-spectrum, non-selective herbicide. It is intended for professional use in the control of present weeds in non-crop situations, pre-planting, pre-sowing, pre-emergence of crops and post-crop emergence with directed/protected spray in tree and field crops. It is not intended for use in home garden. The proposed use patterns are presented in Document D1. The toxicological properties and risk assessment of the active ingredient, paraquat, are evaluated in this document. The majority of the data for paraquat was provided with the dossier submitted to the EU Commission for review under Directive 91/414/EEC, and formed the basis of Annex I inclusion (Commission Directive 2003/112/EC). The endpoints based on these data are summarized in SANCO/10382/2002 rev 9.

IIIA 7.1 Acute Toxicity

Summary of acute toxicity

Paraquat 200 g/l SL Formulation A3879FA: Summary of Acute Toxicity

Parameter	Species	Results	Reference
Acute oral	Rat	Females 550 mg/kg	Pooles A, 2005a
Acute dermal	Rat	Males & Females >2000 mg/kg	Pooles A, 2005b
Acute inhalation	-	-	Clapp M, 2003
Skin irritation	Rabbit	Irritant	Pooles A, 2005d
Eye irritation	Rabbit	Non Irritant	Pooles A, 2005d
Skin sensitisation - Buehler test	Guinea pig	Not a sensitiser	Moore G, 2005

IIIA 7.1.1 Oral

Report:	IIIA 7.1.1/01 Pooles A (2005a). Paraquat 200 g/l SL formulation (A3879FA): Acute Oral Toxicity In The Rat – Up And Down Procedure. Safepharm Laboratories Limited, UK. Syngenta Unpublished Report No. SPL 006/666. Dates of experimental work: 11 July 2005 – 14 September 2005. (Syngenta File No. PP148/2530).
Guidelines:	OECD 425 (2001): OPPTS 870.1100 (2002)
Deviations:	None. The study met all the criteria specified in the guidelines detailed in 92/69/EEC.
GLP:	Yes (certified authority)

Materials and methods: Paraquat 200 g/l SL formulation (A3879FA); actual ai content 202 g/l paraquat ion (corresponding to 18.2% w/w), 1.55 g/l PP796 (corresponding to 0.14% w/w); formulation number A3879FA; batch reference number SMU5EP001.

Test System: A total of nine young adult female Sprague-Dawley CD (Crl: CD® (SD) IGS BR) rats were given a single oral dose of paraquat 200 g/l SL formulation (A3879FA). The test substance was dosed as supplied for the 2000 and 550 mg/kg doses and was prepared as a solution in distilled water for the 175 mg/kg dose, the dose volume ranged from 0.50 – 1.82 ml/kg bodyweight. The rats were fasted overnight prior to dosing and were observed for 14 days following dosing. The rats were dosed in sequence with at least 48 hours between each animal. Bodyweights were recorded at intervals during the study and all animals were given a gross examination *post mortem* at the end of the observation period.

Table IIIA 7.1.1-1 : Dosing regime and outcome

Dosing sequence	Animal number	Sex dosed	Dose level (mg/kg)	Outcome
1	1	Female	175	Survived
2	2	Female	550	Survived
3	3	Female	2000	Died
4	4	Female	550	Killed *in extremis*
5	5	Female	175	Survived
6	6	Female	550	Survived
7	7	Female	2000	Killed *in extremis*
8	8	Female	550	Survived
9	9	Female	2000	Died

Findings:

General observations: Two animals treated at a dose level of 2000 mg/kg were found dead and one animal treated at a dose level of 2000 mg/kg was killed *in extremis* one or two days after dosing. One animal treated at a dose level of 550 mg/kg was killed *in extremis* four days after dosing. There were no deaths noted at a dose level of 175 mg/kg.

Hunched posture was noted in one animal treated at a dose level of 175 mg/kg and all animals treated at a dose level of 550 or 2000 mg/kg. Ataxia and/or pilo-erection were also noted in three animals treated at a dose level of 550 mg/kg and all animals treated at 2000 mg/kg. Other incidents of systemic toxicity noted were lethargy, tip-toe gait, decreased respiratory rate, laboured and noisy respiration, pallor of the extremities, emaciation, dehydration and hypothermia. One animal dosed with 2000 mg/kg was comatose one day after dosing. Pale faeces were noted in two animals at 550 mg/kg. There were no signs of systemic toxicity in the animal dosed at 175 mg/kg.

The surviving animals showed expected gains in bodyweight over the study period except for one animal dosed at 550 mg/kg which showed bodyweight loss during the first week but expected gain in bodyweight during the second week.

Gross pathology: Abnormalities noted at necropsy of animals that died or were killed *in extremis* during the study were abnormally red lungs, dark liver or patchy pallor of the liver, dark kidneys, gaseous stomach or green coloured material present in the stomach, epithelial sloughing of the gastric mucosa and non-glandular region of the stomach. No abnormalities were noted at necropsy of animals killed at the end of the study.

Conclusion: The acute oral LD_{50} (and 95% confidence limits) of paraquat 200 g/l SL formulation (A3879FA) to female rats is 550 (380-1710) mg/kg bodyweight (based on an assumed sigma of 0.5).

IIIA 7.1.2 Percutaneous

Report:	IIIA7.1.2/01 Pooles A (2005b). Paraquat 200 g/l SL formulation (A3879FA): Acute Dermal Toxicity In The Rat. Safepharm Laboratories Limited, UK. Syngenta Unpublished Report No. SPL 006/667. Dates of experimental work: 21 July 2005 – 4 August 2005. (Syngenta File No. PP148/2509)
Guidelines:	OECD 402 (1987): OPPTS 870.1200 (1998): 92/69/EEC B.3 (1992)
Deviations:	None. The study met all the criteria specified in the guidelines detailed in 92/69/EEC.
GLP:	Yes (certified authority)

Materials and methods: Paraquat 200 g/l SL formulation (A3879FA); actual ai content 202 g/l paraquat ion (corresponding to 18.2% w/w), 1.55 g/l PP796 (corresponding to 0.14% w/w); formulation number A3879FA; batch reference number SMU5EP001.

Test System: A group of five male and five female Sprague-Dawley CD (Crl: CD® (SD) IGS BR) rats was given a single, 24-hour, semi-occluded dermal application of undiluted paraquat 200 g/l SL formulation (A3879FA) to intact skin at a dose level of 2000 mg/kg bodyweight. The volume of the dose was 1.82 ml/kg. The test substance was evenly dispersed on the skin (approximately 10% of the total body surface area), covered with a gauze-lined semi-occlusive dressing fastened around the trunk of the animal with an adhesive elastic bandage. After exposure, the dressing was removed and the skin cleaned with cotton wool moistened with 3% Teepol followed by water. The animals were fitted with a collar until day 7 following removal of residual test substance. Animals were observed for mortality and signs of systemic toxicity frequently on the day of dosing and then daily for 14 days. Irritation was assessed and scored according to Draize (1977). The rats were weighed immediately before application of the test substance and on days 7 and 14 prior to sacrifice and examined *post mortem.*

Findings:
General observations: There were no deaths and no signs of systemic toxicity. Very slight erythema was noted at eight treatment sites during the study. Crust formation, which prevented evaluation of erythema and oedema, small superficial scattered scabs and glossy skin were also noted. Six treatment sites appeared normal 13 days after treatment. All animals showed expected gains in bodyweight over the study period except for one male and three females which showed a bodyweight loss during the first week and expected gain in bodyweight during the second week of the study.

Gross pathology: No abnormalities were noted at examination *post mortem.*

Conclusion: The acute dermal LD_{50} of paraquat 200 g/l SL formulation (A3879FA) to male and female rats is in excess of 2000 mg/kg.

IIIA 7.1.3 Inhalation

Report:	IIIA7.1.3/01 Clapp MJL (2003). Paraquat: Lack of potential for inhalation toxicity from aqueous formulations; Syngenta Central Toxicology Laboratory, unpublished. (Syngenta File No. ASF378/0030).
Guidelines:	Toxicology Position Statement not following any specific guideline
Deviations:	Not relevant
GLP:	No

An acute inhalation toxicity study is not required for paraquat 200g/l SL formulation A3879FA on the basis of the conditions set out in the Commission Directive 94/79/EC amending Council Directive 91/414/EEC. Paraquat dichloride is non-volatile and formulations containing paraquat are not applied through equipment, which would generate a significant proportion (> 1% w/w) of spray droplets of diameter less than 50µm.

Further in considering the Classification under the Dangerous Preparations Directive (1999/45/EEC), Article 6 ('Evaluation of health hazards') states in paragraph 3, that "where it can be demonstrated by .... statistically backed evidence ... that toxicological effects on man differ from those suggested by the application of the methods outlined in paragraph 1, then the preparation shall be classified according to its effects on man"

Paraquat is highly toxic to rats following inhalation but only when exposed to highly respirable particles, when the droplet size is increased the toxicity is reduced.

Human passive dosimetry studies have shown that inhalation exposure to paraquat is negligible and this has been confirmed in biomonitoring studies where only very low levels of human exposure have been found. Furthermore, the inhalation potential of respirable droplets was found to be negligible since no respirable paraquat could be measured in the breathing zone of exposed workers even under difficult spraying conditions. Hence a large margin of safety exists between a potential lethal dose and the detected level of exposure to spray operators.

Inhalation exposure is not a prominent feature in human paraquat poisoning cases because of the extremely low ($1x10^{-9}$ mm Hg) vapour pressure of paraquat. It is therefore not surprising that there are no reports in the published literature of deaths arising from inhalation exposure. A review of 30 cases of presumed inhalation exposure found no evidence for systemic poisoning.

Therefore, since there is negligible or no inhalation exposure to paraquat: paraquat 200 g/l SL formulation (A3879FA) should not be classified as very toxic by inhalation under required under DPD (1999/45/EEC).

IIIA 7.1.4 Skin irritation

Report:	IIIA7.1.4/01 Pooles A (2005c). Paraquat 200 g/l SL formulation (A3879FA): Acute Dermal Irritation In The Rabbit. Safepharm Laboratories Limited, UK. Syngenta Unpublished Report No. SPL 006/668. Dates of experimental work: 12 July 2005 – 22 August 2005. (Syngenta File No. PP148/2532).
Guidelines:	OECD 404 (2002): OPPTS 870.2500 (1998): 2004/73/EC B.4 (2004)
Deviations:	None. The study met all the criteria specified in the guidelines detailed in 92/69/EEC.
GLP:	Yes (certified authority)

Materials and methods: Paraquat 200 g/l SL formulation (A3879FA); actual ai content 202 g/l paraquat ion (corresponding to 18.2% w/w), 1.55 g/l PP796 (corresponding to 0.14% w/w); formulation number A3879FA; batch reference number SMU5EP001.

Test System: One male and two female, young adult, New Zealand White, rabbits were given a dermal application of 0.5 ml of Paraquat 200 g/l SL formulation (A3879FA) to an area approximately 2.5 cm x 2.5 cm on a shaved area of the flank. The formulation was applied on a gauze cotton patch, secured with a strip of surgical adhesive tape and the trunk of the rabbit was wrapped in an elasticated corset. The dressing was removed after 4 hours and any residual formulation was removed with cotton wool soaked in 3% Teepol.

The Draize scale (Draize, 1959[1]) was used to assess the degree of erythema and oedema at the application sites approximately 1 hour, 1, 2 and 3 days after removal of the dressings and then at intervals up to 27 days until all sites appeared normal. Mean erythema and oedema scores were calculated. Bodyweights were recorded at the start and end of the study.

Findings: A single 4-hour semi-occluded application of paraquat 200 g/l SL formulation (A3879FA) to the intact skin of three rabbits produced well-defined erythema and slight oedema. Loss of skin elasticity, moderate desquamation and crust formation, which prevented evaluation of erythema and oedema, glossy skin and reduced regrowth of fur were also noted. One animal appeared normal at the 21 day observation, one other animal appeared normal at the 22-day observation and the remaining treated animal appeared normal at the 27 day observation. Increased salivation was present in one animal at the 48 and 72 hour reading and bodyweight loss was also noted in one animal during the study.

[1] Draize (1959) "Dermal Toxicity" In: Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. Association of Food and Drug Officials of the United States, Austin, Texas, p.47.

Table IIIA 7.1.4-1: Individual and mean skin irritation scores of Paraquat 200 g/l SL formulation (A3879FA) according to the Draize scheme

Time	Erythema			Oedema		
Animal number	**124**	**11**	**12**	**124**	**11**	**12**
after 1 hour	2s	2s	2s	1	2	2
after 24 hours	2s	2s	2s	2	2	2
after 48 hours	2	2s	2s	2	1	1
after 72 hours	2	2s	2s	1	1	1
mean score 24-72 h	2.0	2.0	2.0	1.7	1.3	1.3
after 7 days	2Cf	2sD	2sLe	1	1	1
after 10 days	1Cf	?eCf	?eCf	0	?od	?od
after 14 days	1DFr	0DFr	?eCf	0	0	?od
after 17 days	0G	0DFr	?eCf	0	0	?od
after 21/22 days	0	0	0CfFr	0	0	0
after 24 days	-	0	0CfFr	-	0	0
after 27 days	-	0	0	-	0	0

s pale green-coloured staining; Cf crust formation; D moderate desquamation; Le loss of skin elasticity; ?e adverse reactions preventing evaluation of erythema; ?od adverse reactions preventing evaluation of oedema; Fr reduced regrowth of fur; G glossy skin

Conclusion: Paraquat 200 g/l SL formulation (A3879FA) produced a primary irritation index of 3.5 and was classified as a moderate irritant to rabbit skin according to the Draize classification system.

IIIA 7.1.5 Eye irritation

Report:	IIIA7.1.5/01 Pooles A (2005d). Paraquat 200 g/l SL formulation (A3879FA): Acute Eye Irritation In The Rabbit. Safepharm Laboratories Limited, UK. Syngenta Unpublished Report No. SPL 006/669. Dates of experimental work: 1 August 2005 – 6 September 2005. (Syngenta File No. PP148/2531).
Guidelines:	OECD 405 (2002): OPPTS 870.2400 (1998): 2004/73/EC B.5 (2004)
Deviations:	None. The study met all the criteria specified in the guidelines detailed in 92/69/EEC.
GLP:	Yes (certified authority)

Materials and methods: Paraquat 200 g/l SL formulation (A3879FA); actual ai content 202 g/l paraquat ion (corresponding to 18.2% w/w), 1.55 g/l PP796 (corresponding to 0.14% w/w); formulation number A3879FA; batch reference number SMU5EP001.

Test System: Paraquat 200 g/l SL formulation (A3879FA) (0.1ml) was instilled into one eye of each of three (one male and two female) New Zealand White albino rabbits and an assessment of initial pain was made. The eyes were examined 1, 24, 48 and 72 hours after instillation of paraquat 200 g/l SL formulation (A3879FA) and the grade of ocular reaction was assessed according to the Draize scale. The eyes were examined for up to 21 days, to assess the grade of ocular reaction. The numerical scores were used to classify the eye irritation potential of the formulation using a modified form of the system described by Kay and Calandra.

Findings:
General observations: Immediately following instillation into the eye all the animals had a slight initial pain reaction (2 on a 0-5 scale). The formulation contains green dye and green-coloured staining of the fur was noted around all treated eyes during the study. No corneal or iridial effects were noted. Minimal conjunctival irritation was noted in all treated eyes one hour after treatment and at the 24, 48 and 72-hour observations and in one treated eye at the 7 and 14-day observations. Fur loss around the treated eye was noted in two animals at the 14 day and 17 day observations. All signs of irritation had disappeared in one animal at the 17 day observation and in two animals at the 21 day observation.

Increased salivation was noted in all animals at the 48 hour, 72 hour and 7 day observations and persisted in two animals at the 10, 14 and 17 day observations.

Table IIIA 7.1.5-1: Eye irritation scores of Paraquat 200 g/l SL formulation (A3879FA) according to the Draize scheme

Time	Cornea			Iris			Conjunctiva					
							Redness			Chemosis		
Animal number	13	46	47	13	46	47	13	46	47	13	46	47
after 1 hour	0	0	0	0	0	0	1	1	1	0	1	1
after 24 hours	0	0	0	0	0	0	1	1	1	0	1	1
after 48 hours	0	0	0	0	0	0	1	1	1	1	1	1
after 72 hours	0	0	0	0	0	0	1	0	0	1	0	0
mean scores 24-72h	0	0	0	0	0	0	1	0	0.7	0.7	0.7	0.7
after 7 days	0	0	0	0	0	0	1	0	0	0	0	0
after 10 days	-	0	0	-	0	0	-	0	0	-	0	0
after 14 days	0	0	0	0	0	0	0	0	0	0	0	0
after 17 days	0	0	0	0	0	0	0	0	0	0	0	0
after 21 days	-	0	0	-	0	0	-	0	0	-	0	0

Conclusion: Paraquat 200 g/l SL formulation (A3879FA) was classified as a mild irritant (class 4 on a 1-8 scale) to the rabbit eye according to a modified Kay and Calandra classification system.

IIIA 7.1.6 Skin sensitization

Report:	IIIA 7.1.6/01 Moore G (2005). Paraquat 200 g/l SL formulation (A3879FA): Dermal Sensitisation Study in Guinea Pigs (Buehler Method) with Paraquat 200 g/l SL Formulation (A3879FA). Product safety Laboratories, 2394 Highway 130, Dayton, NJ 08810, US. Syngenta Unpublished Report No. 17726. Dates of experimental work: 26 June 2005 to 5 August 2005. (Syngenta File No. PP148/2535).
Guidelines:	OECD 406 (1992): OPPTS 870.2600 (2003): 96/54/EC B.6 (1996)
Deviations:	None. The study met all the criteria specified in the guidelines detailed in 92/69/EEC.
GLP:	Yes (certified authority)

Materials and methods: Paraquat 200 g/l SL formulation (A3879FA); actual ai content 202 g/l paraquat ion (corresponding to 18.2% w/w), 1.55 g/l PP796 (corresponding to 0.14% w/w); formulation number A3879FA; batch reference number SMU5EP001.

Test System: The sensitisation potential of the test substance was assessed using a method based on that described by Ritz and Buehler (1980). Groups of 20 test and 10 control young adult female Hartley albino guinea pigs were used for the main study. Two main procedures were involved; (a) the potential induction of an immune response; (b) a challenge of that response.

In test animals, the induction phase involved the topical application of 0.4 ml of a 10% w/w preparation of paraquat 200 g/l SL formulation (A3879FA) in distilled water, on a lint patch 2cm x 2cm, under an occlusive dressing to a shorn area of the lower left flank. Dressings were left in place for 6 hours. After the 6-hour exposure period, the patches were removed and the sites gently cleansed of any residual test substance. The induction process was repeated at the same site during the next two weeks giving a total of nine 6-hour exposures, three per week. Approximately 24 and 48 hours after each induction application, any erythema was assessed using a 0-3 scale.

Control animals were maintained under the same environmental conditions, but no induction applications were made.

In the challenge phase, 28 days after the first induction application, two lint patches, each 1 x 2 cm, were used. Approximately 0.2 ml of a 1% w/w mixture of paraquat 200 g/l SL formulation (A3879FA) in distilled water was applied to the first patch and a similar volume of a 0.3% w/w preparation in deionised water was applied to the second patch. The patches were held in place by an occlusive dressing for 6 hours. Test and control animals were treated identically.

Skin sites were examined 1 and 2 days after removal of the dressings and erythema was scored according to a 0-3 scale where scores of 1 or above are considered to be positive reactions.

A positive control study was conducted using essentially the same methodology and using alpha-hexylcinnamaldehyde (HCA) as the test substance. The test substance was applied undiluted in the induction phase (3 induction applications only, 7 days apart) and as 75% and 50% preparations in mineral oil for the challenge phase.

To classify a test substance as a potential contact sensitiser, $\geq$15% of the test animals exhibit a positive response (scores > 0.5) in the absence of similar results in the vehicle control.

Findings:
General observations: All animals survived, gained bodyweight and appeared active and healthy during the study.

During the induction phase, very faint to faint erythema (scores of 0.5 – 1) was noted for all test sites.

Following challenge with a 1% preparation of the formulation in distilled water, very faint erythema (score 0.5) was noted for 7 out of 20 test sites and 3 out of 10 control sites 24 hours after challenge. Irritation persisted at one of the test sites for 48 hours.

Following challenge with a 0.3% preparation of the formulation in distilled water there was no erythema seen at any site, test or control.

Based on these findings and the evaluation system used, there were no positive sensitisation responses and, therefore, paraquat 200 g/l SL formulation (A3879FA) is considered not to be a skin sensitiser.

In the positive control study, following challenge with 75% HCA in mineral oil faint to moderate erythema (1-2) was seen in 9 out of 10 test animals 24 hours after challenge, which persisted as faint erythema (1) at the 48 hour reading. Very faint to faint erythema (0.5-1) was seen in 3 of the controls. Following challenge with 50% HCA in mineral oil, 4 out of 10 animals exhibited faint erythema after 24 and 48 hours and very faint erythema (0.5) was present in 1 of 5 controls at the 24 hour reading only. The positive response observed in the positive control study validates the test system.

Table IIIA 7.1.6-1: Buehler test: Number of animals with positive signs of allergic skin reactions (erythema score ≥ 1) following challenge

	Test flank			
	Challenge at 1%		Challenge at 0.3%	
Scored after:	24 hours	48 hours	24 hours	48 hours
Main test – test group	0/20	0/20	0/20	0/20
Main test - vehicle control	0/10	0/10	0/10	0/10
	Challenge at 75%		Challenge at 50%	
Positive control – test group	9/10	8/10	4/10	4/10
Positive control – vehicle control	1/5	0/5	0/5	0/5

Conclusion: Paraquat 200 g/l SL formulation (A3879FA) is considered not to be a contact sensitiser.

IIIA 7.1.7 Supplementary studies for combinations of plant protection products

Further data related to the toxicokinetics of paraquat in dogs are provided in this section. These studies are not related to combinations of plant protection products but are supplementary to the basic set of acute toxicity data.

As part of a commitment to work to introduce formulations of paraquat that are of reduced hazard compared with existing formulations, Syngenta has undertaken an extensive research programme to try to improve the safety of paraquat formulations, including oral toxicity. Over the last seven years this effort has been focused on the use of a novel formulation technology (INTEON) based on alginate derived from the *Ascophyllum* seaweed as an agent to hold the formulation in the stomach and allow effective emesis. This specific project led to the development of A3879FA.

Paraquat is known to be more readily absorbed from the small intestine, particularly the jejunum, than either the oesophagus or the stomach (*Heylings, 1991*[2]). One focus to reduce the oral toxicity of paraquat is therefore to reduce the exposure of the small intestine to ingested material.

Alginates are carbohydrates of polymannuronic and polyguluronic acid, are non-toxic, and are commonly used in the food industry as gelling agents. They are also used in the pharmaceutical industry for their therapeutic properties, for example in treating dyspepsia (*Mandel et al, 2000*[3]) and wound healing (*Agren, 1996*[4]). For INTEON, an alginate that gels under low pH conditions (pH 1-3) was selected. This material therefore remains liquid and flowable as a formulation in normal use, but if it is swallowed and reaches the acidic conditions of the stomach, it forms a semi-solid gel. This change holds the material in the stomach, and allows emesis to be more effective in removing the semi-solid material than it would be in removing a liquid.

This would reduce the amount of any ingested paraquat that might be released to the small intestine, the site of greatest absorption for paraquat. Further, the inclusion of magnesium sulphate, a known purgative (*Schiller, 1999*[5]), should further reduce the absorption of any paraquat reaching the small intestine by stimulating purgation of any material leaving the stomach.

Within Commission Directive 2003/112/EC it is specified that Member States must ensure that technical concentrates shall contain an effective emetic. The technical concentrate manufactured by Syngenta at Huddersfield or Bayport contain PP796 which has been demonstrated to be an effective emetic previously discussed in the Appendix to Document M-II Section 3 submitted to the EU Commission for review under Directive 91/414/EEC. Liquid formulations shall contain an effective emetic, blue/green colourants and stenching and other olfactory alerting agent or agents. Other safeners, such as thickeners, may also be included. The formulation, A3879FA conforms to the FAO specification (2003) and contains the emetic, blue green colourant and an alerting agent as described in Document J.

It has been demonstrated that A3879BU, a similar formulation to A3879FA (as described in Document J), but with a built-in-wetter system results in a low level of gastrointestinal absorption of paraquat following oral ingestion in a vomiting species, the dog. The new 200g/l INTEON formulation showed a low level of paraquat absorption and no lethalities at dose levels expected to be lethal with the 200g/l Gramoxone formulation (A3879D) currently marketed in many regions of the world, . This indicates in the dog, a vomiting species, a clear improvement in the safety of A3879BU formulation and predictably A3879FA, compared to the standard Gramoxone formulation. Syngenta consider that the available results indicate that these paraquat formulations (A3879BU and A3879FA) would be expected to provide a significant reduction in the amount of paraquat absorbed in humans.

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

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

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

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

Toxicokinetics of A3879BU in the dog

Report:	IIIA7.1.7/01 Brammer A (2004). Paraquat 200 g/l SL Formulation (A3879BU): Toxicokinetic Study In The Dog. Central Toxicology Laboratory, UK. Syngenta Unpublished Report No. CTL/XD7201/REGULATORY/REPORT. Report issue date: 7 January 2004. Dates of experimental work: 30 April 2003 (initiated), 6 May 2003 to 6 October 2003 (in-life phase). (Syngenta File No. PP148/1856)
Guidelines:	Investigative, non guideline study
Deviations:	Not applicable as this was an investigative, non guideline study
GLP:	Yes (certified authority)

Materials and methods: Test material: Paraquat 200 g/l SL formulation (A3879BU); actual concentration 203 g/l paraquat ion and 1.56 g/l emetic PP796; formulation number A3879BU; batch reference number J6481/016.

A group of three male beagle dogs received oral doses (by capsule) of paraquat 200 g/l SL formulation (A3879BU), on 5 occasions at monthly intervals. The nominal dose levels used were 8, 16, 32, 64 and 128 mg paraquat ion/kg. Allowing for specific gravity and purity, these doses were equivalent to achieved dose levels of 46, 92, 184, 368 and 736 mg A3879BU formulation/kg.

Following each dose, the dogs were observed continuously for 4 hours and then frequently during the remainder of the day. All incidences of emesis were recorded and vomit and faeces were removed immediately to prevent possible re-ingestion. Blood samples were taken at intervals following each dose to enable a plasma profile of paraquat and PP796 (the emetic included in the formulation) to be determined. Veterinary examinations (including cardiac and pulmonary auscultation) were made prior to each dose and prior to termination. General clinical observations, bodyweights and food consumption were measured at weekly intervals throughout the study. Clinical pathology parameters were measured from blood samples taken prior to and then 24 hours after each dose. At the end of the study period, the animals were killed and examined *post mortem*. Specified tissues were taken for subsequent histopathological examination.

Findings:
General observations: The dose levels of paraquat ion and of A3879BU formulation received by each dog are presented below:

Table IIIA 7.1.7-1: Overall mean dose received (mg/kg/day)

Nominal dose level (mg paraquat ion/kg	Dose volume (ml formulation/kg)	Achieved dose[a] (mg formulation/kg)
8	0.04	46
16	0.08	92
32	0.16	184
64	0.32	368
128	0.64	736

a - mg formulation/kg = $\frac{\text{(dose volume [ml] x 1.15 [specific gravity]) x 1000}}{\text{weight (kg)}}$

The principal clinical findings were emesis and the times to first and last emesis are shown below:

Time to first emesis:

Achieved Dose Level of A3879BU (mg Paraquat ion/kg)	Dog No. 1	Dog No. 2	Dog No. 3	Mean time to first emesis
46 (8)	68 minutes	36 minutes	50 minutes	51.3 minutes
92 (16)	41 minutes	28 minutes	37 minutes	35.3 minutes
184 (32)	31 minutes	23 minutes	24 minutes	26 minutes
368 (64)	29 minutes	44 minutes	21 minutes	31.3 minutes
736 (128)	23 minutes	16 minutes	22 minutes	20.3 minutes

Time to last emesis:

Achieved Dose Level of A3879BU (mg Paraquat ion/kg)	Dog No. 1	Dog No. 2	Dog No. 3
46 (8)	88 minutes	66 minutes	67 minutes
92 (16)	95 minutes	42 minutes	46 minutes
184 (32)	72 minutes	101 minutes	60 minutes
368 (64)	65 minutes	77 minutes	59 minutes
736 (128)	127 minutes	75 minutes	133 minutes

With increasing doses of the paraquat formulation (and hence, increasing dose of emetic) the time to first emesis generally reduced to approximately 20 minutes post dosing and the duration of emesis and quantity of vomit increased. The time to emesis was delayed for Male 2 following the 368 mg formulation/kg dose, to 44 minutes (compared with 21 and 29 minutes for the other 2 dogs) but this is considered to be due to delayed absorption of the emetic due to the presence of faecal material in the stomach.

Additional clinical signs of slightly decreased activity, restlessness and/or excessive salivation were present following the 184 and 368 mg formulation/kg doses but, at 736 mg formulation/kg (dose 5), these signs were more pronounced and were accompanied by more frequent bouts of retching and/or vomiting, which were more frequent at the early time points but persisted for up to 2¼ hours after dosing. Male 3 had slightly decreased activity 2 days after dosing at 736 mg formulation/kg in week 18.

The only other clinical observations were the presence of an interdigital cyst from week –1 to week 10 in Male 3. There were no gastro-intestinal abnormalities recorded on "non-dosing" days.

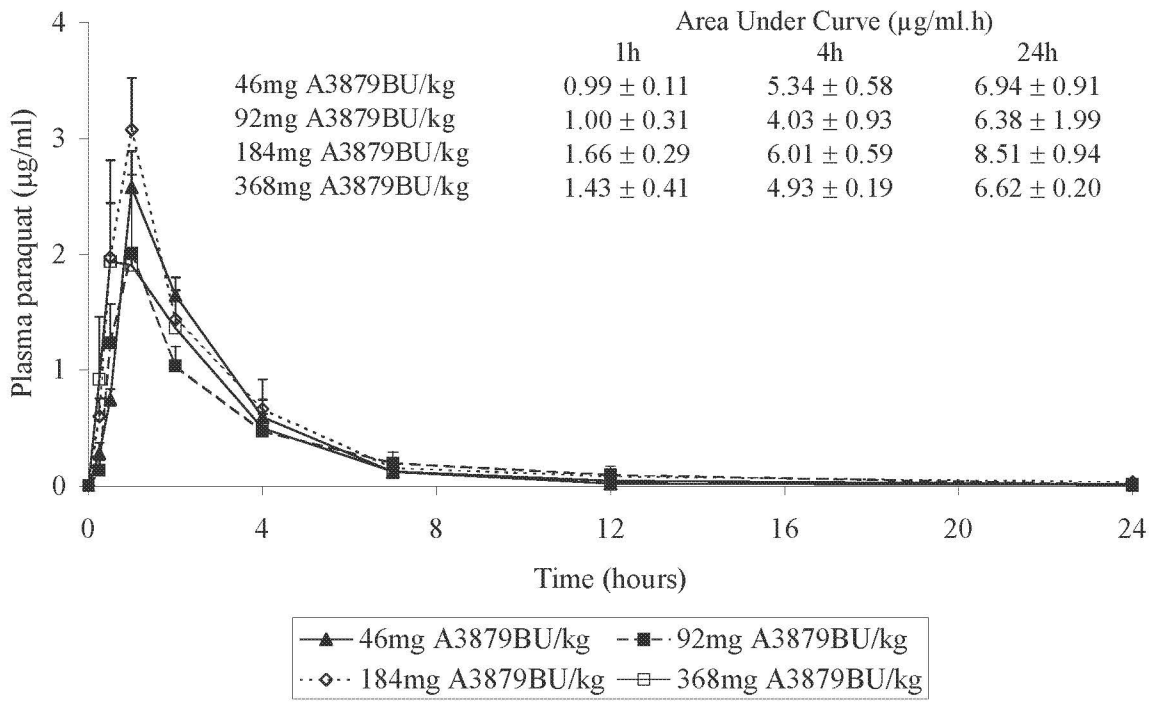
Male 3 regurgitated intact capsules containing the 736 mg formulation/kg dose immediately after dosing (dose 5) and was re-dosed with new capsules approximately 15 minutes later.

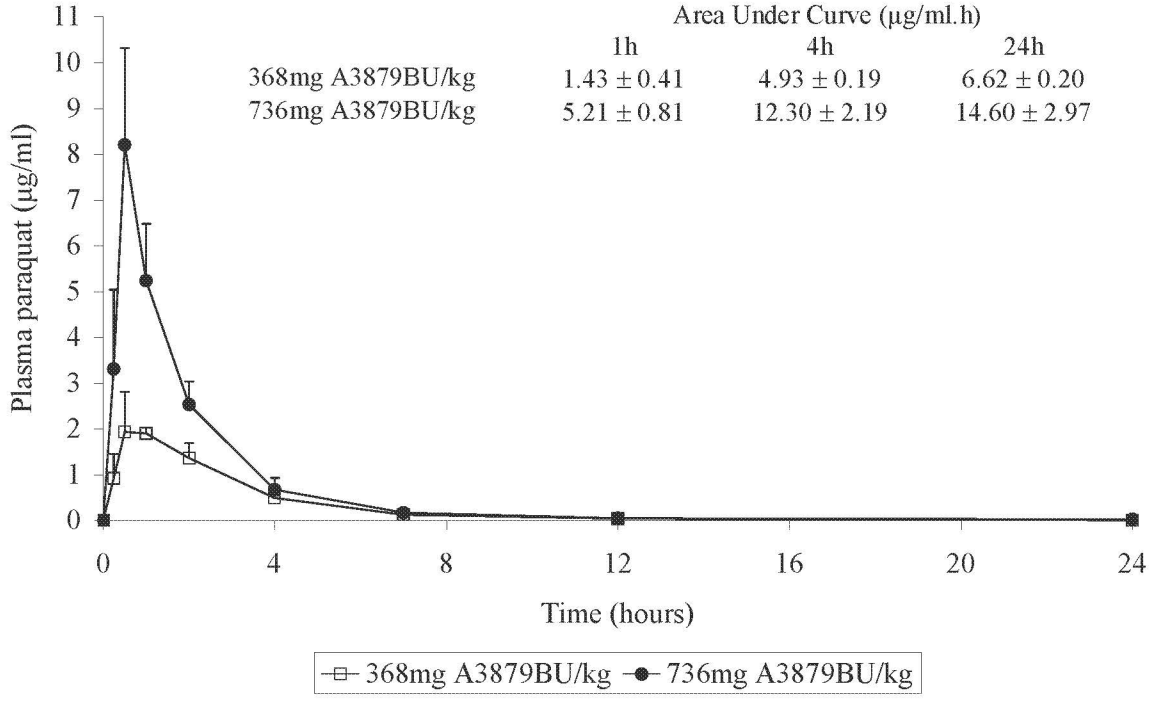
There were no significant findings at any of the veterinary examinations. Male 3 lost 0.5 kg in weight during week 18, following the 736 mg formulation/kg dose. This was considered to be a consequence of the inappetance apparent in this animal during week 18 following dosing. Food consumption returned to normal during week 19.

Clinical pathology: There were no treatment-related changes in any of the clinical chemistry parameters assessed.

Toxicokinetics:
Paraquat ion: The mean plasma concentrations of paraquat are shown graphically in figure IIIA 7.1.7-1.

Figure IIIA 7.1.7-1: Mean plasma paraquat concentrations





Values shown are the means ± SEM

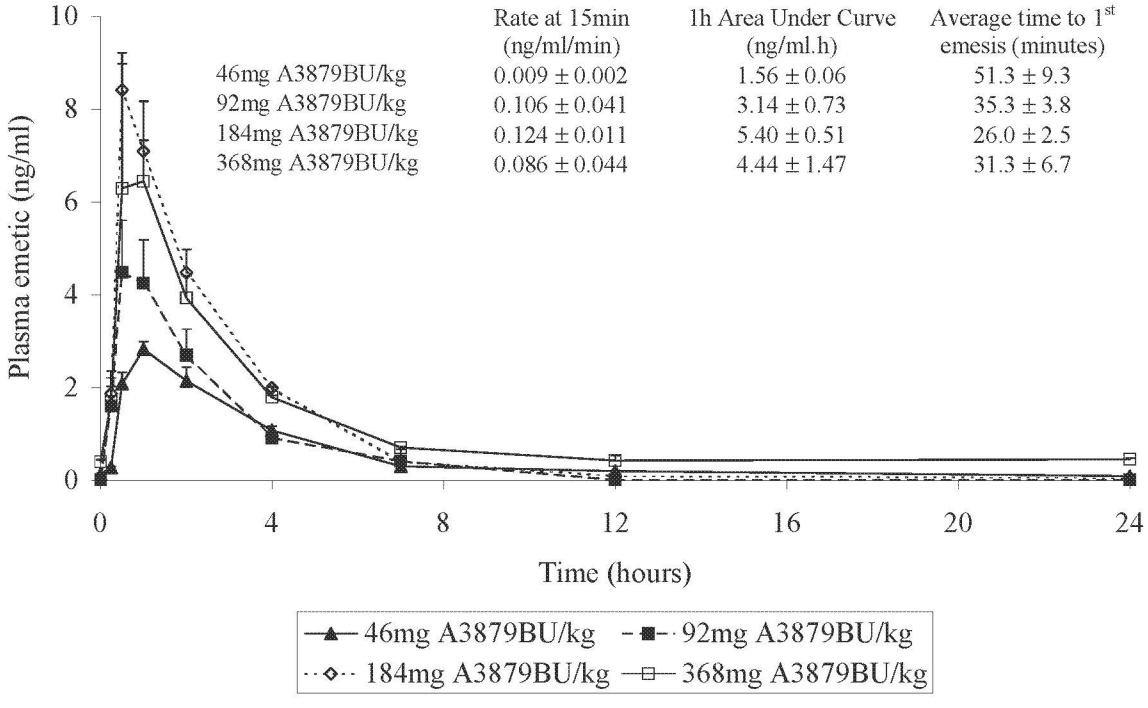
When animals received doses between 46 and 368 mg formulation/kg (equivalent to 8 and 64 mg of paraquat ion/kg), the plasma profile was similar with peak levels of between 2-3 µg paraquat ion/ml occurring at 30 minutes -1 hour post dose. There was no evidence of a dose response with regards to plasma levels of paraquat between 46 and 368 mg formulation/kg. This is reflected by the relatively consistent area under the curve values at 1, 4 and 24 hours.

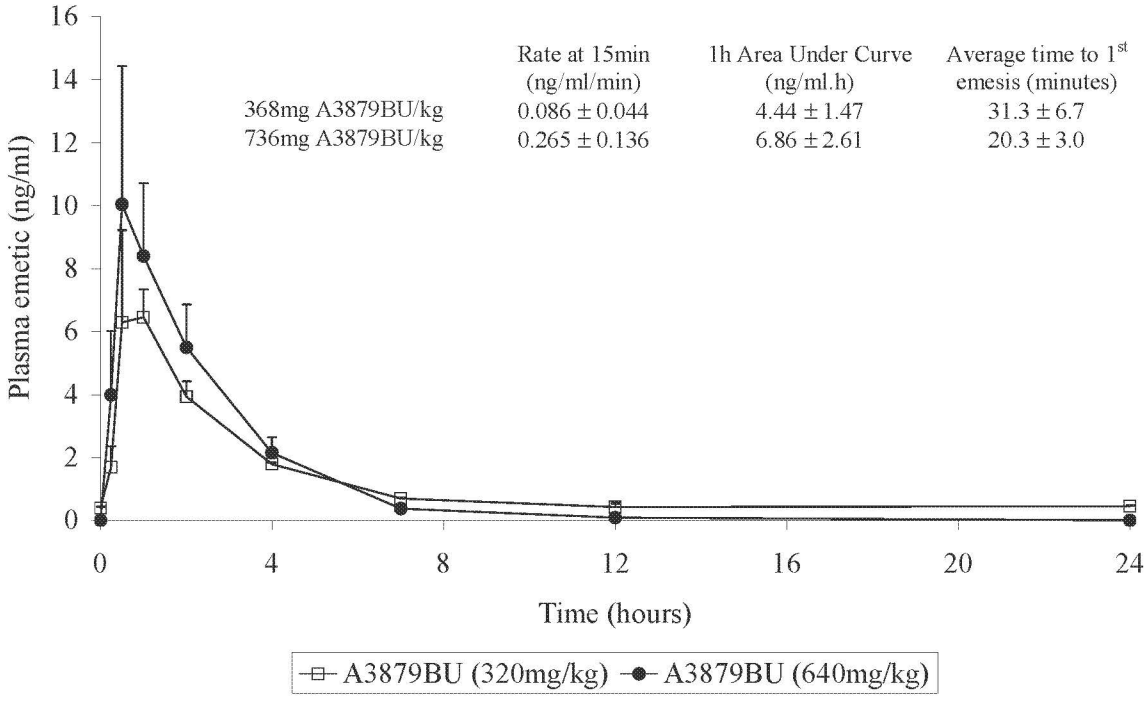
When the dose of A3879BU was increased to 736 mg formulation/kg (equivalent to 128 mg paraquat ion/kg), the plasma profile altered such that the peak concentration occurred at 30 minutes with a mean peak value of 8.21 ± 2.11 µg/ml. The levels of paraquat fell quite rapidly, so that at 4 hours post-dose the plasma levels were similar to those observed with lower doses. This profile indicates that there was a higher initial absorption of paraquat but these levels were not sustained, probably as a result of the early emesis. This higher, early absorption of paraquat at 736 mg formulation/kg increased the AUC values at 1, 4 and 24 hours to approximately double that observed with the lower doses.

For male 3 following the 736mg formulation/kg dose, the plasma paraquat concentration was considerably lower at 15 minutes than that of the other 2 dogs and was then much higher at 30 minutes post dose. It is possible that the initial regurgitation of the dosing capsules altered the stomach environment so the re-dosed capsules were dissolved more slowly than usual.

Emetic: The mean plasma concentrations of emetic (PP796) are shown graphically in Figure IIIA 7.1.7-2.

Figure IIIA 7.1.7-2: Mean plasma emetic concentrations





Values shown are the means ± SEM

The emetic plasma profile showed a dose response at the majority of the doses used, the only exception being a slightly high plasma concentration at 184 mg formulation/kg (equivalent to 32 mg paraquat ion/kg) than at 368 mg formulation/kg (equivalent to 64 mg paraquat ion/kg).

However, this was influenced by Male 2 where absorption of the emetic may have been delayed due to the presence of faecal material in the stomach.

After administration of 46 mg formulation/kg (equivalent to 8 mg paraquat ion/kg), the peak plasma emetic levels was 1 hour after dosing whilst with all the higher doses, peak plasma emetic concentrations were at 30 minutes after dosing. The general pattern is a rapid absorption of emetic after dosing which steadily fall up to 7 hours post dose. Between 7 and 24 hours there was a measurable but low level of emetic in the plasma. Examination of the initial rate of absorption over the first 15 minutes shows an increase in the rate of absorption with increasing doses of formulation, again there was an exception with the 368 mg formulation/kg (equivalent to 64 mg paraquat ion/kg) dose, as mentioned previously.

Gross pathology: Two of the three dogs showed no abnormalities. One dog (number 3) had dark spots or areas (<5mm diameter) on the left apical and cardiac lobes of the lung.

Histopathology: The lungs of two of the dogs were normal. In male 3, there was slight focal interstitial fibrosis, slight focal alveolar macrophage infiltration and slight focal pneumonocyte hypertrophy indicative of paraquat toxicity.

Minor spontaneous changes (minimal medullary calcification) were present in the kidneys of 2 of the dogs (males 2 and 3). The kidneys of the third dog were normal.

Conclusion: Doses of 46-736 mg A3879BU formulation/kg, equivalent to 8-128 mg paraquat ion/kg, were well tolerated in the dog. This demonstrates in the dog, a vomiting species, a low level of paraquat absorption at doses up to 736mg A3879BU/kg. Following this dose the dogs showed no clinical effects although one out of three animals showed slight changes in the lungs indicative of paraquat toxicity. The lethal dose of the INTEON formulation A3879BU and predictably A3879FA is greater than 736mg /kg.

Toxicokinetics of Gramoxone (A3879D) in the dog

Report:	IIIA7.1.7/02 Heylings J, Swain C and Brammer A (2004). Paraquat: Gramoxone 200 g/l Formulation – Toxicokinetics In The Dog. Central Toxicology Laboratory, UK. Syngenta Unpublished Report No. CTL/026118/RESEARCH/REPORT. Report issue date: 28 January 2004. Dates of experimental work. XD1236 - 12 March 1987 (first dose) to February 1989, XD1328 – 27 October 1987 (first dose) to May 1992 (Syngenta File No. ASF378/0059)
Guidelines:	Investigative, non guideline study
Deviations:	This was an investigative, non guideline study
GLP:	Yes (certified authority)

Materials and methods: Test material: Gramoxone SL formulation (200 g/l paraquat ion) A3879D. Purity: 20% w/v paraquat ion and 0.5 g/l emectic (PP796) assumed.

Data have been extracted from a series of studies in the dog, conducted at Central Toxicology Laboratory between 1987 and 1991, which compared the absorption of paraquat from different novel paraquat formulations with that of the commercial product, Gramoxone. The data extracted from these studies provide a plasma profile following oral administration of Gramoxone (a 200g paraquat ion/l formulation) at a nominal dose of 8mg paraquat ion/kg, administered by gavage or

gelatine capsule. Allowing for purity and specific gravity, this was equivalent to 44mg formulation/kg. This dose was chosen since it is just below that used in the paper of Widdop et al, (1977) where a dose of 55mg Gramoxone/kg (equivalent of 10mg paraquat ion/kg) was shown to be lethal to all dogs. The exact composition of the formulation used by Widdop et al was not reported other than being a UK Gramoxone formulation and hence may not have contained emetic.

Beagle dogs were dosed with Gramoxone at a dose volume of 0.04ml/kg, to achieve the required oral dose of 8mg paraquat ion/kg, based on the most recent bodyweight. Gramoxone was dosed to groups of 3 or 4 dogs on several occasions either by capsule or gavage, with intervals of at least 4 weeks between doses.

All dogs were observed continuously for the first few hours following each dose. The timing, colour, consistency of vomit and faeces were recorded, in addition to other clinical signs. On non-dosing days, dogs were observed at least twice daily for clinical or behavioural abnormalities (at the beginning and the end of the working day). Gastro-intestinal findings were assessed daily throughout the study. All dogs were given a full clinical examination by a veterinarian prior to each dose and prior to termination.

All dogs were weighed before feeding, on a weekly basis throughout the study. Food residues were recorded 24 hours after feeding and any residual food was discarded. Food was withheld on the day of dosing. Food consumption was recorded throughout the study and was calculated at weekly intervals as a mean value (g food/day) for each dog.

Blood samples were taken to determine a toxicokinetic profile of paraquat ion following each dose of Gramoxone formulation. Jugular vein blood samples were taken from each dog pre-dose and at 15 and 30 minutes and 1, 2, 4, 7, 12 and 24 hours after dosing. The blood was thoroughly mixed and then the plasma was separated by centrifugation. Plasma concentrations of paraquat were determined by radioimmunoassay. The unknown sample and a series of paraquat standards were each buffered with [^{3}H]-paraquat. Antiserum containing antibodies, raised against a derivative of monoquat, was added. After a short incubation time any free paraquat ion was adsorbed onto a bovine serum albumin-charcoal suspension. After centrifugation, the antibody-[^{3}H]-paraquat ion complex in the supernatant was counted in a liquid scintillation counter and the concentration of paraquat ion in the sample was found by comparison with the standards.

The plasma profile of paraquat over 24 hours was determined and the mean (± SEM) concentrations from all the dogs within each dose group (n=3 or n=4) were calculated.

The toxicokinetic parameter, area under the curve (AUC) was calculated using the linear trapezoidal rule from pooled groups of animals. The toxicokinetic parameters AUC_{0-1}, AUC_{0-4} and AUC_{0-24} (area under the curve between time zero and 1, 4 and 24 hours respectively) were calculated.

Findings:

General observations: The specific gravity of Gramoxone, as defined by the manufacturing specification for a 200g/l Gramoxone formulation, was 1.07-1.10g/ml. Therefore, assuming a specific gravity of 1.10g/ml, a dose of 8mg of paraquat ion/kg (either by capsule or by gavage) would equate to animals having received the equivalent of 44mg Gramoxone formulation/kg, when administered at 0.04ml formulation/kg, as follows:

$$\text{mg formulation/kg} = \frac{(\text{dose volume [0.04ml]} \times \text{specific gravity [1.1]}) \times 1000}{\text{weight (kg)}}$$

Figures IIIA 7.1.7-3 and IIIA 7.1.7-4 show the mean plasma paraquat concentrations for each occasion that Gramoxone was administered to dogs by either capsule (Figure IIIA 7.1.7-3) or gavage (Figure IIIA 7.1.7-4). The mean plasma concentrations of paraquat are shown graphically in Figure IIIA 7.1.7-5.

Examination of these plasma profiles illustrates that following administration of Gramoxone the profile was very similar between different groups of dogs and when administered in a capsule or by gavage. Due to the good reproducibility of the results in small groups of animals, only the combined data set for each administration route will be discussed.

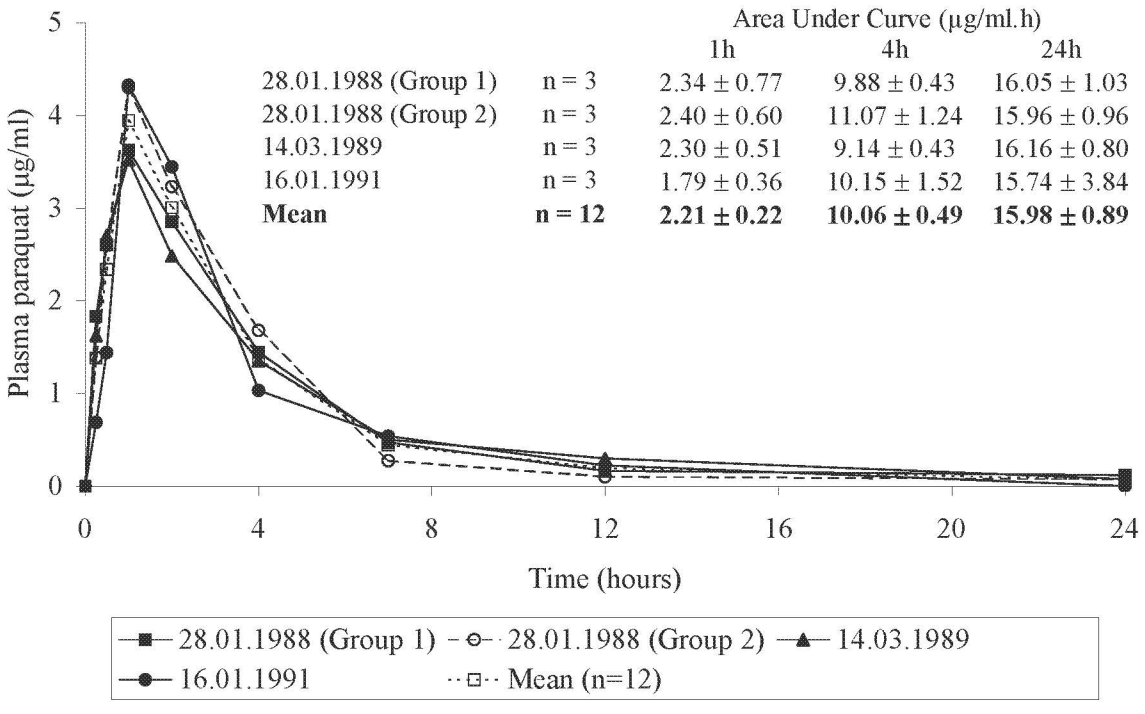
The general plasma paraquat profile showed mean peak plasma concentrations of between 3.5 and 4µg/ml, occurring at 1 hour after dosing, for capsule and gavage administration respectively. After this plasma paraquat levels gradually fell to around 0.4µg/ml at 7 hours. This level fell further to around 0.2µg/ml at 12 hours and was still measurable at 24 hours.

The plasma paraquat profile following either capsule or gavage administration of Gramoxone resulted in very similar AUC values throughout the 24h period (Figures IIIA 7.1.7-3 and IIA 7.1.7-4). Following administration of Gramoxone by capsule, the AUC values were calculated as 4.18 ± 0.26, 12.13 ± 0.94, 16.38 ± 0.94µg/ml.hour at 1, 4 and 24 hours respectively. Administration of Gramoxone via gavage resulted in slightly lower AUC values of 4.05 ± 0.23, 10.65 ± 0.73 and 15.78 ± 1.28µg/ml.hour at 1, 4 and 24 hours respectively.

There were no statistically significant differences between the two methods of oral dosing. Furthermore, the plasma paraquat concentrations were below that which causes acute toxicity in this species and all dogs were clinically normal following this dose of paraquat.

Figure IIIA 7.1.7-3 – Mean plasma paraquat concentrations following capsule administration of Gramoxone

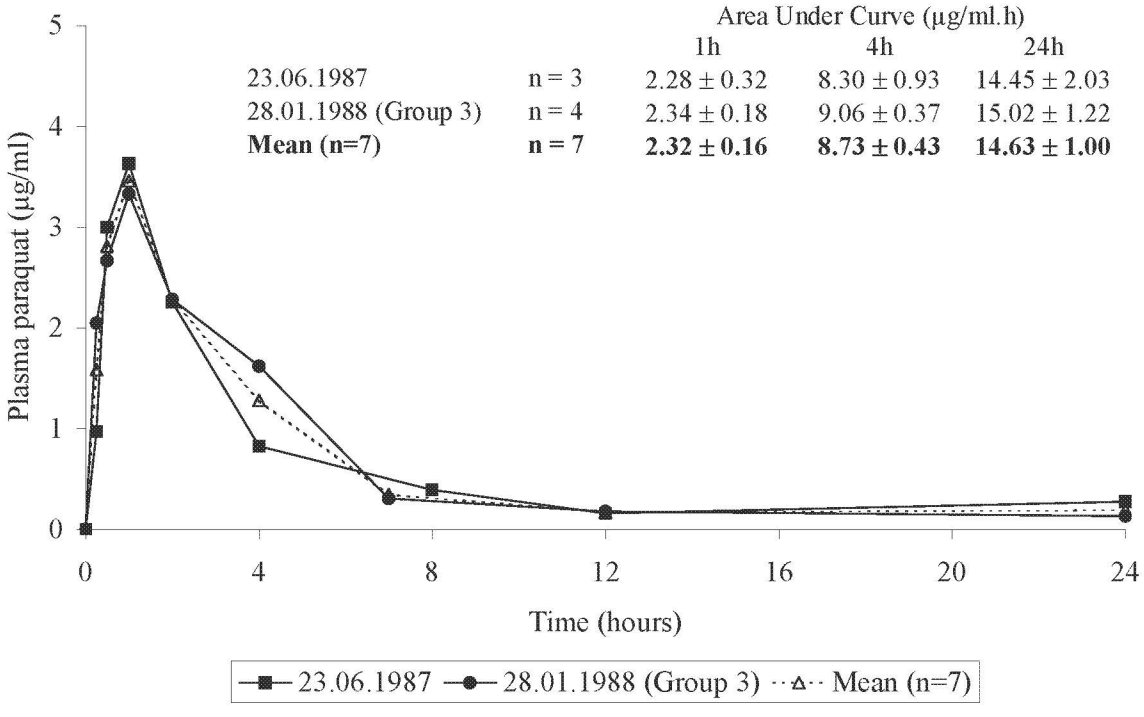
Capsule administration of 44mg Gramoxone/kg



Values shown are the means ± SEM
Groups of 3 dogs were orally dosed with Gramoxone by capsule.
The specific gravity as defined by the manufacturing specification for a 200g/l Gramoxone formulation was 1.07 and 1.10g/ml.
Calculations have assumed a specific gravity of 1.10g/ml.

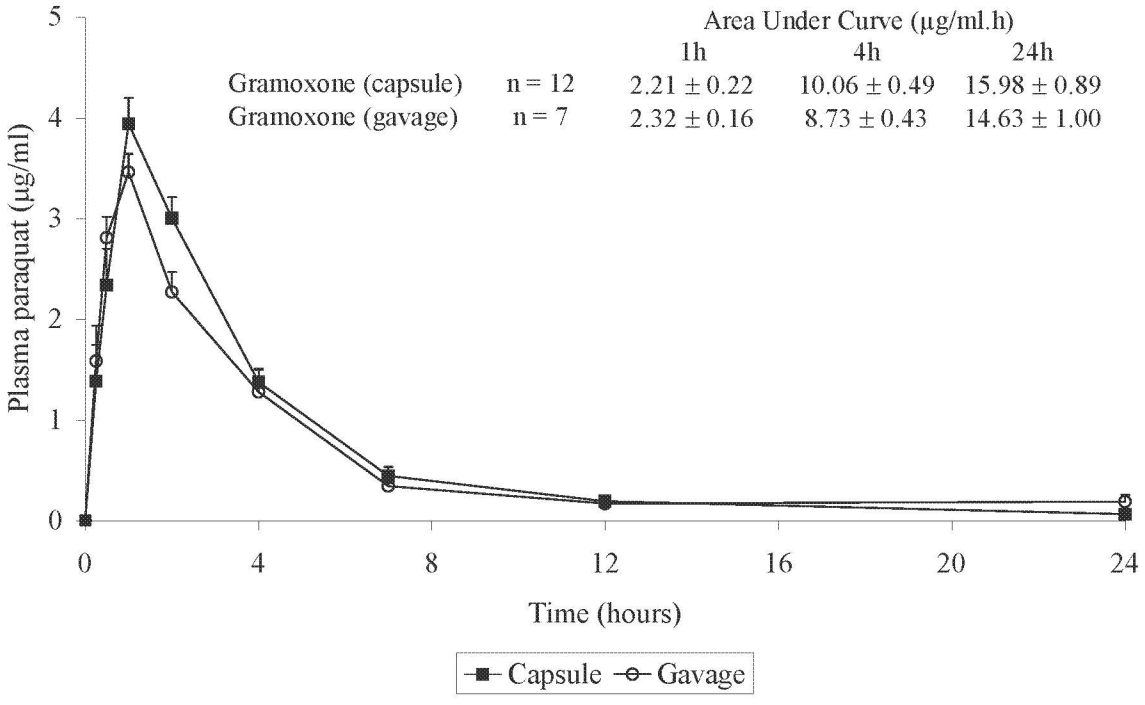
Figure IIIA 7.1.7-4 – Mean plasma paraquat concentrations following gavage administration of Gromoxone

Gavage administration of 44mg Gramoxone/kg



Values shown are the group means ± SEM
A group of 3 dogs (23.06.1987) and a group of 4 dogs (28.01.1988) were orally dosed with Gramoxone by gavage.
The specific gravity as defined by the manufacturing specification for a 200g/l Gramoxone formulation was 1.07 and 1.10g/ml.
Calculations have assumed a specific gravity of 1.10g/ml.

Figure IIIA 7.1.7-5 – Comparison of mean plasma paraquat concentrations following capsule or gavage administration of gramoxone



Values shown are the means ± SEM.
Group sizes were n=12 (derived from four groups of 3 animals) for capsule dose and n=7 (derived from a group of 3 and a group of 4 animals) for gavage dose.
The specific gravity as defined by the manufacturing specification for a 200g/l Gramoxone formulation was 1.07 and 1.10g/ml. Calculations have assumed a specific gravity of 1.10g/ml.

There were no signs of acute toxicity following these single doses of Gramoxone. Vomiting, in response to capsule or gavage administration of Gramoxone, was present on at least 1 occasion in 13 out of 19 doses. There were no obvious differences in response between the capsule or gavage administration. There were no clinical observations other than vomiting and there were no signs of toxicity observed following these doses.

In those which vomited, the time to first emesis varied between 16 minutes and 50 minutes and the duration of vomiting was generally short with only 1 or 2 incidences, except for one dog, which vomited 4 times. After approximately 1 hour after dosing there was generally no further observations of vomiting. The exceptions to this were one dog where clear vomit was only observed 2 hours 25 minutes after dosing and another dog where a pool of brown vomit was present 4 hours 11 minutes after dosing. In both these instances, the dogs had been normal at 1 hour post dose and these later observations are considered to be incidental to treatment with Gramoxone.

A slight bodyweight loss was observed in some dogs in the week following dosing with Gramoxone, but this probably reflects the absence of food on the day of dosing. There was no effect on food consumption in any of the dogs in the week following dosing.

There were no delayed signs of toxicity following these doses of Gramoxone and all dogs remained on study for further evaluation of paraquat formulations until termination some months or even years later, at the scheduled end of the studies.

Conclusion: Oral administration of 44mg/kg Gramoxone formulation (A3879D), equivalent to 8mg paraquat ion/kg, was well tolerated in the dog. Mean peak plasma levels ranged between 3.5 and 4µg/ml at 1 hour after dosing and the overall mean 24 hour AUC was approximately 15µg/ml.hour. An emetic response occurred in most cases on at least 1 occasion, within 1 hour of dosing. There were no signs of acute or delayed toxicity following these single doses of Gramoxone.

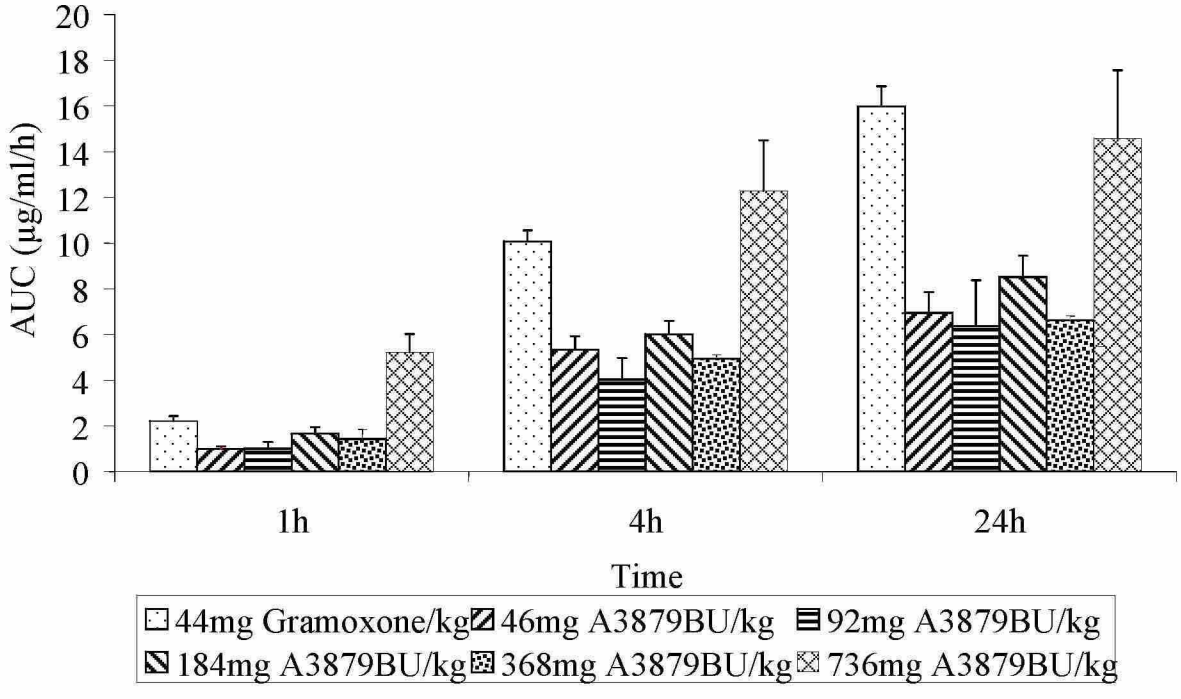
Comparison of the kinetic toxicity data in the dog for the new INTEON formulation A3879BU and the current Gramoxone formulation (A3879D).

This section compares the toxicokinetics in the dog from a range of doses (46 to 736mg/kg) of a 200g/l paraquat INTEON formulation, A3879BU (Brammer, 2004) with the results from a non-toxic dose (44mg/kg) of Gramoxone (Heylings, Swain and Brammer 2004). This dose was chosen since it is just below that used in the paper of Widdop et al (1977) where a dose of 55mg Gramoxone/kg (equivalent to 10mg paraquat ion/kg) was shown to be lethal to all dogs. Although the exact composition of the formulation used by Widdop et al was not reported other than being a UK Gramoxone formulation and hence may not have contained emetic, the current evaluations have examined Inteon formulations at greater than 10 times this dose level (128mg paraquat ion/kg) with no lethalities. Both sets of results are described above.

Following oral doses of up to 368mg A3879BU lower levels of paraquat absorption were observed compared with those following an oral dose of 44mg Gramoxone /kg. In the dogs exposed to 736mg A3879BU formulation/kg (16 fold higher than the Gramoxone dose), the initial peak plasma paraquat levels were higher than those at other doses. This was only transient and plasma level of paraquat dropped to below that of the 44mg Gramoxone formulation/kg by 2 hours.

This is confirmed by the area under the curve (AUC) calculations, which show lower values for all INTEON formulation doses at 24 hours compared to Gramoxone at 44mg formulation/kg. AUC's of 40µg/ml/h. or greater or a peak plasma paraquat well above 10µg/ml, in combination with adverse clinical signs are indicators of paraquat toxicity and would lead to the removal of the animal from the study.

Figure IIIA 7.1.7-6 Plasma paraquat AUC values following an oral dose of A3879BU (46 - 736mg formulation/kg b wt.) in dogs (n = 3) in comparison with Gramoxone



In conclusion the oral toxicity of the proposed 200g/l INTEON formulation A3879BU, and predictably A3879FA, show limited levels of absorption of paraquat and no lethalities following oral ingestion even up to 736 mg formulation/kg.

Syngenta consider that the available results indicate that INTEON technology would be expected to provide a significant reduction in the amount of paraquat absorbed following oral ingestion, and hence the acute toxicity in humans.

IIIA 7.2 Short-Term Toxicity

This is not an European Community (EC) data requirement

IIIA 7.3 Operator Exposure

Foreword

The present operator exposure assessment includes uses in Belgium, Czech Republic, Cyprus, Greece, Italy and Malta. To a certain extent, spray volumes differ between countries. Model estimates are based on the uses in Belgium which correspond to the worst case with regard to in-use concentrations. The assessed application rate of 1 kg a.i./ha also corresponds to one of the highest use rates.

Since in most cases the model based exposure estimates exceed the AOEL the risk assessment is based on the Tier III biomonitoring exposure studies. Specific calculations of somewhat more favourable country specific use conditions would not bring additional information.

Operator Exposure

During the review of paraquat for Annex I inclusion, the potential effects of paraquat on operators were discussed and within Commission Directive 2003/112/EC it is specified that Member States should pay particular attention to the protection of operators, in particular for knapsack and handheld applications. An assessment of the risk to operators is detailed in this section.

A3879FA (containing 200 g/l paraquat ion as paraquat dichloride) is a contact (post-emergence of the weeds), broad-spectrum, non-selective herbicide. It is intended for use in the control of weeds in non-crop situations, plus pre- and post-crop emergence in orchards and field crops. It is not intended for use in home garden. Most herbicide applications are normally done with spray volumes of up to 200 l/ha. In view of paraquat's biological mode of action (a contact product that destroys all green parts of plants reached by the spray), farmers take the necessary precautions to avoid:

- spray drift on to neighbouring crops,
- droplet impact on the green parts of the crops in which weeds are being controlled (mainly in vines and arboriculture).

To avoid drift and the formation of small droplets, farmers adjust their sprayers suitably (low pressure: < 1 bar, high water volume: 300 to 500 l/ha and boom positioned low) and in some cases, they use protective screens to prevent the green parts of plants being reached. Application is not permitted using broadcast air-assisted application equipment or ultra low volume applications. Treatment is recommended when there is little or no wind.

For knapsack sprayer applications, the equipment is also adjusted to deliver droplets that are large enough not to drift. As it is a herbicide being applied, the nozzle is pointed downwards, which limits exposure of the upper parts of the body.

The proposed classification for A3879FA is proposed as R22 'Harmful if swallowed' and R38 'Irritating to skin'.

The proposed recommendation for PPE (personal protective equipment) for the use of A3879FA is:

- Coveralls, face shield and impermeable gloves during mixing/loading and when handling the spray boom or adjusting nozzles.

- Coveralls and face shield during spraying.

Applications in field crops are often made in winter or early spring (weed control in dormant alfalfa crops – soil preparation for crops sown in early spring). At that time of year, farmers naturally wear warm clothing that protects the whole of their bodies, particularly overalls or long trousers and long-sleeved jackets, boots or heavy shoes. Typically, the tractor is equipped with a cabin.

The proposed package size is: 1, 5 L HDPE bottle.

Table IIIA 7.3-1: Use pattern

Crop/situation	Min/max water rate (L/ha)	Min/max application rate (kg as/ha)	Remarks
CZ-Republic			
Celeriac, Onion, Garlic, Dill, Water-melon, Sugar melon, Carrot Cucumber, Parsley, Tomato, Radish, Lettuce, Maize, Marjoram –herb, Potatoe Sugar beet, Beet	400	0.4-0.6	
Forest and Forest nursery	300-500	0.8-1.0	Row application
Grape	600	1.0-1.1	
Hop	600	0.4	
Land not for farming	400-600	0.8-1.1	
Orchards	600	1.0-1.1	
Spinach	400	0.4-0.8	
Strawberry	600	0.8-1.1	Row application
Italy and Malta (details in Document D1)			
Seed bed/transplanting bed preparation	600-1000	max 1.1kg /year	
Vines	600-1000	max 1.1kg /year	Inter-row and sucker control
Citrus	600-1000	max 1.1kg /year	Inter-row
Stone fruit	600-1000	max 1.1kg /year	Inter-row
Pome fruit	600-1000	max 1.1kg /year	Inter-row
Tree nuts	600-1000	max 1.1kg /year	Inter-row and ring treatment
Olives	600-1000	max 1.1kg /year	Inter-row and ring treatment
Non-cropped areas	600-1000	max 1.1kg /year	
Cyprus and Greece			
Tree corps Citrus, pome friut, stone fruit, nuts, olives, Grapes, Kiwi,	600-800	0.4-1 max 1.1kg as/year if 2 applications	Spray the whole land against the weeds, or direct spray around the trees, or in bands. The bole must be completely wooden.
Solanaceae: - Tomato - Aubergine - Pepper	600-800	0.4- 0,6 max 1.1kg /year if 2 applications	Directed spray between the rows. Height of weeds<10cm
Vegetables **Leaf vegetables, Legume vegetables**, Pulses	600-800	0.4- 0,6	Directed spray between the rows. Height of weeds<10cm
Field crops: Maize, potatoe, sugar beets, tobacco, Cotton, cereals, trefoil,	600-800	0.4- 0,6 max 1.1kg /year if 2 applications	Directed spray between the rows. Height of weeds<10cm
Uncultivated land	600-800	0.8 max 1.1kg as/year if 2 applications	Spray weeds when height<10-15cm.
Belgium			
Temporary non-cropped agriculture soils	300 - 500	1) 0.6 - 1	In stubbles or spring cleaning
Permanent non-cropped area (hard and non-hardened surfaces)	300 - 500	1) 0.6 – 1 *	*Also knapsack sprayer use possible at max. 50ml/ 10L water/ 100m² (0.5%)
Field borders (Use not linked to a specific crop)	300 - 500	1) 0.6 - 1	To limit the spread of undesirable weeds
Ware and early potatoes,	300 - 500	1) 0.4 - 1	In tank mix with a residual selective herbicide. Preferably at the latest by first shoots appearing (10-20% max)
Seed potatoes	300 - 500	1) 0.4 - 1	In tank mix with a residual selective herbicide. Treat at the latest 1 day before emergence
Asparagus	300 - 500	1) 0.6 - 1	Treat immediately after harvest and before appearance of new shoots.
Clover	300-500	1) 0.3 - 0.4	During dormancy (December – February)
Clover	300-500	1) 0.5 - 0.6	Immediately after cutting
Lucerne	300-500	1) 0.3 - 0.4	During dormancy (December – February)
Lucerne	300-500	1) 0.5 - 0.6	Immediately after cutting
Fruiting trees and shrubs (> 3 years)	300 - 500	1) 0.6 - 1 *	Treatment with a residual herbicide possible. *Also knapsack sprayer use possible at max. 50ml/ 10L water/ 100m² (0.5%)
Fruiting trees and shrubs (new plantation, max. 3 years old trees)	300 - 500	1) 0.5 - 1 Max. 1100 g as/year if 2 applications *	*Also knapsack sprayer use possible at max. 50ml/ 10L water/ 100m² (0.5%)
Ornamental shrubs	300 - 500	1) 0.6 - 1	Treatment with a residual herbicide possible.

IIIA 7.3.1 Estimation of operator exposure assuming personal protective equipment is not used

Acceptable Operator Exposure Level for Paraquat

The exposure pattern of paraquat is considered to be short-term at specific periods during a year and not continuous exposure throughout the year. Data indicate that paraquat is rapidly cleared from the body with >90% excreted within 72 hours (refer to **Document M-II Section 3** and **SANCO/10382/2002 rev 9**). The endpoint summary indicates that the lung is the main target organ and states some potential for accumulation in the lungs. However, there is no evidence from the comparison of 1 year and 90 day NOAELs in the dog where these reflect dose levels selected for studies. It is therefore appropriate to use a short/medium term systemic AOEL for the assessment of paraquat. Paraquat is not directly toxic to reproduction in rats and mice. The dog is the most sensitive species to the general toxicological effects and the AOEL for paraquat, given in the review report, is based on the NOAEL of 0.56mg/kg bw/d from the 13 week dog study. From the absorption, distribution, metabolism and excretion studies on paraquat a value of 10% oral absorption is appropriate and a 100 fold uncertainty factor is applied to give:

$$\text{AOEL} = \frac{0.56 \text{ mg/kg bw/day} \times 10\%}{100} = \underline{\mathbf{0.0005 mg/kg\ bw/d}}$$

A long-term systemic AOEL of 0.0004 mg/kg bw/d is also proposed in **SANCO/10382/2002 rev 9** based on the 1 year dog study corrected for 10% oral absorption, however it is considered that this is not relevant for the short-term, occasional use regime currently proposed. The use of a short-term (90 day) systemic AOEL is supported in the **Addendum to the Draft Report for paraquat (monograph), May 2000**.

Operator exposure estimates were calculated using both the German model[6] and the UK-POEM[7].

The following assumptions and parameters have been used in calculation of operator exposure:

Dermal absorption in human skin	• 0.075 % for the undiluted product and • 0.323 % for the spray dilution.
AOEL	• 0.0005 mg/kg b.w.
Use rates	• Tractor application: 1 kg a.i./ha in 300L of water (maximum recommended use rate /concentration) • Knapsack application: 1000 g a.i./300L of water*
Container sizes used:	• Vehicle mounted boom sprayers: 5 L, (it is assumed that for the treatment of 10 ha per day which requires the total of 50 L product the typical bottle size used is 5L • Knapsack sprayers 1 L

[6] Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protections); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirschaft, Berlin-Dahlem, n° 277

[7] Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel. Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM) (UK MAFF) 1992.

Operator exposure estimates are calculated in **Appendix 1**: The results of the operator exposure estimates and their corresponding risk quotients (RQ) are presented in IIIA 7.3.1.-1. The risk quotient is defined as:

$$RQ = \frac{systemic\ exposure\ (mg/kg\ b.w)}{AOEL\ (mg/kg\ b.w)}$$

Table IIIA 7.3.1.-1: Estimates of Systemic Exposures and Risk Quotient using the German and UK Model

A3879FA		Total Systemic Exposure mg/kg b.w.		Risk Quotient (systemic exposure mg/kg bw/AOEL)	
		German Model	UK POEM	German Model	UK POEM
Vehicle mounted boom sprayers	no PPE[1)]	0.0029	0.012	5.7	24.1
Knapsack sprayers	no PPE[1)]	No data	0.025	No data	50.94

[1] No PPE:
German model: shorts, short sleeved shirt
UK-POEM: long sleeved shirt, long trousers "permeable". No gloves during mixing and loading.

Vehicle mounted boom sprayer

German model: Assuming the highest recommended use rate of 1 kg a.i./ha the estimated operator exposure exceeds the established AOEL (0.0005 mg/kg b.w.) by a factor of about 6 (rounded figures) for the unprotected operator.

UK-POEM: Assuming the highest recommended use rate of 1 kg a.i./ha and the lowest recommended spray volume of 300L/ha, the estimated operator exposure exceeds the established AOEL by a factor 24.

Knapsack Application:

UK-POEM: The estimated operator exposure exceeds the AOEL (RQ about 51)

IIIA 7.3.2 Estimation of operator exposure assuming personal protective equipment is used

Table IIIA 7.3.2.-1: Estimates of Systemic Exposures and Risk Quotient using the German and UK Model

A3879FA		Total Systemic Exposure mg/kg b.w.		Risk Quotient (systemic exposure mg/kg bw/AOEL)	
		German Model	UK POEM	German Model	UK POEM
Vehicle mounted boom sprayers	PPE[2)]	0.0009	0.0109	1.8	21.8
	PPE[3)]	0.0004	0.00118	0.81	2.36
Knapsack sprayers	PPE[2)]	No data	0.025	No data	50.04
	PPE[3)]	No data	0.00375	No data	7.5

[2] PPE: German model: Coverall, hat, solid shoes and during mixing loading impermeable gloves

UK-POEM long sleeved shirt, long trousers "permeable. Gloves are worn during mixing and loading
[3] PPE: UK-POEM: Coverall, hat, solid shoes, during mixing loading and application: impermeable gloves and respiratory mask
German Model: Coverall, hat, solid shoes, impermeable gloves during all operations and during mixing/loading respiratory mask

Vehicle mounted boom sprayer

German model: When wearing protective clothing according to label recommendation the, estimated operator exposure still exceeds the AOEL by a factor of about 2. Only when assuming the additional use of a respiratory mask during mixing/loading and gloves also during application (i.e. when direct contact to contaminated surfaces is given) the estimated operator exposure is within the established AOEL (81% of AOEL).

UK-POEM: Assuming the highest recommended use rate of 1 kg a.i./ha and the lowest recommended spray volume of 300L/ha, the estimated operator exposure exceeds the established AOEL (0.0005 mg/kg b.w.) and results in RQs of 21. When assuming protective clothing, gloves and respiratory protection the estimated operator exposure is still exceeding the AOEL by a factor of about 2.4.

Knapsack Application:

UK-POEM: For all scenarios assessed the estimated operator exposure exceeds the AOEL (RQ about 51 to 7.5)

Conclusion:

These estimates of operator exposure show that under most standard conditions the AOEL is exceeded in the context of tractor use and for all conditions during the use of knapsack sprayers.

It is recognised that model estimates lead to conservative results. This generally is a consequence of the characteristics of passive dosimetry studies, which are the basis of the models. In addition the following factors add to this over-estimation of exposure:

- Matrices to collect residues (operators underwear or patches worn inside the clothing) in those studies are of cotton material and they should represent the operator's skin. However, cotton has a much higher absorption potential than skin, so taking these residue values as the true skin deposit and correcting it with the factors for dermal absorption leads to very conservative assumptions on systemic exposure.

- Differences in statistics and quality and study design of the studies selected for the models have further impact on the results of exposure calculations.

- The cumulative conservatism resulting from aggregating 75th percentiles for both mixing and loading activity and application activity, and aggregating the 75th percentiles from each body part, thus creating the 'artificial operator' has a significant impact on the results.

- Another critical point in exposure estimates is the relationship between dermal exposure and percent absorption. The difficulty with this concept is that the percent absorption factor applies only to the applied dose in the dermal absorption study and is not necessarily applicable to all dermal exposures incurred by operators under field conditions. This difficulty is considered to be particularly relevant to slow skin

penetrants, because their absorption is rate-limited, i.e. once the steady state rate of absorption has been reached saturation of the skin with additional exposure will not result in increased absorption.

- The relevance of dermal absorption study design to dermal absorption by the operator is also limited. In reality, the total dermal exposure of the operator is not incurred at 'time zero' but occurs sporadically throughout the working day, building up to the dermal dose that, ideally would have been applied in the dermal absorption study. Therefore, the percent of applied dose measured in the absorption study must over-estimate that which occurs in the operator because of the longer duration of skin contact with the total dose. This would particularly be an issue for slow skin penetrants, which tend to have long 'lag phases' during which the rate of absorption is increasing up to a 'steady state' rate.

- The studies underlying the models are made with many different substances of different volatilities. These characteristics have an influence on the respiratory exposure values measured during mixing/loading of products. Paraquat has a very low vapour pressure (< 1x 10^{-8} kPa at 25 °C) and therefore exposure to vapours can be excluded.

- All predictive models assume 100% inhalation, retention and systemic absorption of the estimated inhalation exposure. Herbicide applications typically require spray volumes of up to 200 L/ha utilising a fine/medium spray. Due to paraquat's biological activity (contact herbicide that destroys all green parts of the plants it touches) extreme care must be taken to ensure that off-target drift is minimized. The spray volume is therefore recommended at 600-800 L/ha utilising large droplets. These droplet sizes are greater than the respirable fraction. Treatment is recommended when there is little or no wind and spray is directed at the ground away from the operator in all cases. The combination of these factors makes exposure to vapour very unlikely. Reduced drift also reduces dermal contamination as a consequence.

The results of the first tier risk assessment using German and POEM modelling conclude that there is a potential concern for operators following the use of A3879FA and therefore further assessment is required.

IIIA 7.3.3 Measurement of operator exposure

The next step within a tiered assessment of the risk to the operator is measurement of either exposure or, where possible, of the absorbed dose via biological monitoring (the latter providing the best possible exposure endpoint for an assessment of operator risk).

Tractor Application:

A paraquat exposure study was conducted in 1994 in the United States (Georgia), in a pecan nut plantation (**Meier, 1995**). This study was considered in the **Draft Report on Paraquat, Volume 3 (monograph)**.

Application was made using a tractor mounted boom sprayer. The parameters of this study as a whole are representative of the conditions of use of the present risk assessment (see Table IIIA 7.3.3 –1)

Table IIIA 7.3.3–1: Conditions of the study and relevance for the present risk assessment

	Conditions of the American study	Relevance to the present risk assessment.
Type of Crop:	Pecan nut plantation	This crop is representative for perennial crops. Since the application technique is a vehicle mounted boom sprayer and the target are weeds growing on the ground, the study can also be used to assess the treatment of field crops.
Concentration	300 g/l	200 g/l
Use rate	Rate of application 1.05 kg/ha of paraquat Spray volume 124-393 L/ha,	This rate covers highest recommended use rates of 1.0 kg a.i./ha, spray volume ≥300 L/ha
Working time:	The study evaluated exposure over a normal, 6-hour working day (4-11 hours), for 17 workers.	This is representative of a treatment in perennial crops.
Work rate	3.3 ha – 30 ha (12 ha) average	This is representative of a treatment in perennial crops in Europe. For field crop application the average daily work rates are assumed to be higher.
Protective equipment during mixing and loading	About half the workers did not wear any special protective equipment or gloves during the mixing/filling operations. Most of the operators were wearing long trousers, boots, a hat and a long- or short-sleeved shirt.	This division with and without protection covers including those scenarios where label recommendations on PPE are not respected.
Protective equipment during application	A large majority of operators did not wear any personal protection equipment or gloves during application. Three operators who were already wearing protective equipment during mixing and filling also wore protective equipment during application.	This division with and without protection covers including those scenarios where label recommendations on PPE are not respected.
Cabin:	None of the tractors used for spraying had a cabin.	Covers the worst case for tractor application with boom sprayers. Mainly in field crop application, tractors have closed cabins, especially when having a work capacity of 50 ha/day.
Boom position:	Some of the tractors had a boom mounted on the side of the tractor compared with those, which had one at the rear of the tractor.	Normally, booms are at the rear of the tractor and often fitted with a screen for applications in perennial crops. For applications in field crops the boom is located at the rear of the tractor. So the scenario monitored is very conservative with regard to use practice in field crops.

The total dose of paraquat absorbed by the operators was measured by collecting 24-hour urine samples on the day of exposure than for the ensuing 5 days. For ease of reference, details of this study, the analytical results and the evaluation of operator risk made on basis of these raw data are set out in Appendix II.

In order to evaluate the operator risk, it is appropriate to separate the 17 operators into two groups, according to their personal protective equipment:

- 9 operators were not wearing any protective equipment during mixing, filling and application. It is in this group that the presence of paraquat was detected in the urine (in 6 of them).

- 8 operators were wearing protective equipment during mixing and filling and sometimes during application. No paraquat was detected in the urine from these 8 people.

Table IIIA 7.3.3–2: Absorbed dose (% of AOEL) measured in the urine of operators using a tractor-mounted sprayer.

	Absorbed dose measured on basis of the field study (% AOEL)	
Tractor with boom	**No protective equipment** (9 operators)	**Protective equipment during mixing/filling and in some cases during application** (8 operators)
	Mean dose absorbed: **0.00015 mg/kg/day** **% AOEL: 30 (9-88)**	Absorbed dose: **0.000071 mg/kg/day** **% AOEL: 14 ***

* Mean value based on a limit of determination in the urine of 5 ng/ml

The absorbed dose measured in this bio-monitoring study during the mixing/filling and spraying phases show that the risk to the operator is acceptable for both groups of operators, under normal conditions of use. The study was sufficiently precise to show a difference according to the means of protection used. In fact, operators who protected themselves in accordance with label recommendations showed a paraquat urine concentration (based on a limit of determination of 5 ng/ml) half as high as that measured in people who had no protective equipment.

The impact of potentially higher daily work rates for field crops than in perennial crops are compensated by the fact that spray booms in field crop applications are always at the rear of the tractor and spray tank. So the distance to the potential source of contamination is significantly larger, than in the study where the majority of the booms have been located at the side of the tractor. Use of a tractor with a closed cabin (which is becoming common practice in field crop application) significantly reduces the operator exposure.

Conclusion: There should be no unacceptable exposure (associated with paraquat absorption) in operators using a tractor-mounted sprayer even in circumstances when protective precautions are not always followed.

Knapsack Application

A number of studies have been conducted that provide information considered relevant to the assessment of operator risk under Greek conditions of use for knapsack.

A knapsack study in Sri Lanka (**Chester, 1989**) is reviewed in the **UK Report on Paraquat (monograph), Volume 3, Sept 1996**.

During the ECCO review, for knapsack application it was considered that the Sri Lankan study was not sufficient as there was no personal protective equipment (PPE) and that over 5 days sampling there were no detects in any of the serum or urine samples at the limit of determination in the study (0.03 µg/ml). For risk assessment purposes, versus the AOEL, the worst-case assumption was that paraquat was present in the urine at a level equivalent to half of the LOQ value of 0.03 µg/ml in every sample over the five days.

The two additional knapsack studies were then submitted from a Spanish study (Findlay, Chester, Wiseman, 1998) and a Guatemalan study (Findlay, 1998) and are reviewed in the **Addendum to the Draft Report for Paraquat (monograph) May 2000** and the **Evaluation Table, Section 4.5, Doc 7755/VI/97**.

The study carried out in Spain (**Findlay, Chester, Wiseman, 1998**) was a realistic assessment of the use of paraquat applied via a knapsack sprayer under representative EU conditions. The workers generally followed the label recommendations for mixing/loading and PPE. The limit of determination (0.75 ηg/ml) was more sensitive than that used for the previous Sri Lankan study.

The Guatemalan study, carried out with diquat, was performed in 1996 on a banana plantation (**Findlay; 1998**). Diquat is a herbicide belonging to the same chemical family as paraquat and is almost identical in its chemical and physical behaviour.

Table IIIA 7.3.3–3: Conditions of the studies and relevance to the conditions to be assessed

Parameters	Parameters of Spanish and Guatemalan studies	Parameters of the study in Sri Lanka	Relevance to the scenarios to be assessed
Product concentration	Product containing 200 g/l paraquat or diquat	Product containing 200 g/l paraquat.	Product containing 200 g/l paraquat.
Use rate	Rate 600-800 g/ha of a.i. according to the amount of water (300-400 litres/ha)	Usual rate: 140 g/ha of a.i. in 450 litres of water/ha , for 5 consecutive days.	0.4 to 1.0 kg a.i./ha in 300 to 1000 L of water
Protective equipment	The operators wore gloves and face protection for mixing and loading. No waterproof coverall worn, nor any special personal protection equipment or gloves during spraying.	None of the operators wore any special personal protection equipment or gloves during mixing/filling and spraying.	Covers the worst case of neglecting label requirements on PPE
Clothing:	The operators wore long trousers, long-sleeved cotton shirts and rubber boots.	The operators wore shorts, short-sleeved shirts. No shoes.	Covers the worst case of neglecting label requirements on PPE

Facial protection consisted of wearing a face shield preventing droplets from splashing in the eyes.

Details of the studies are set out in Appendix 2.

The measurements of the dose absorbed and the percentage of the AOEL are summarised in Table IIIA 7.3.3–4.

Table IIIA 7.3.3–4: Absorbed dose (% of AOEL) measured in the urine of operators using knapsack sprayers

Study	Dose absorbed (mg/kg/day)	Percentage of AOEL
Sri Lanka (paraquat)	**<<< 0.001***	**<<< 200*** no protective equipment, shorts, short-sleeved shirt and no shoes.
Spain (paraquat)	**0.00015** (<LOQ – 0.00041)	**30** (0 - 82) gloves and face protection during mixing/loading. Long trousers, long-sleeved cotton shirt and boots during application.
Guatemala (diquat)	**0.000125** (0.000015 – 0.000589)	**25** (3 - 118) gloves and face protection during mixing/loading. Long trousers, long-sleeved cotton shirt and boots during application.

* This is an overestimate of the dose absorbed because it is based on the hypothesis that paraquat is present in the urine at a level equivalent to half of the LOQ value of 0.03 µg/ml.

Despite the limits of the study performed in Sri Lanka (low sensitivity of the analytical method), there was no paraquat detected despite operator applying Gramoxone for 5 consecutive days, which is consistent with very low paraquat absorption and lack of accumulation.

On the basis of these data it is concluded in the **Addendum to the Draft Report for Paraquat** (monograph) May 2000 and the **Evaluation Table, Section 4.5, Doc 7755/VI/97** that the exposure studies demonstrate that operators handling and using paraquat under the proposed conditions of use, by knapsack or tractor application, will not exceed the AOEL.

Conclusion: These biomonitoring studies demonstrate, under a variety of situations, that the human exposure will not exceed the mean AOEL when applications are made with a knapsack sprayer, under conditions of use, even if the recommendations on the label are not strictly followed.

Health Monitoring Studies

A large number of studies have been published in the medical literature over the last decades regarding the question of long-term effects in human from occupational paraquat ***(Castro-Gutierrez et al, 1997[8], Dalvie et al., 1999[9], Howard. 1980[10], Howard et al., 1981[11], Levin et al., 1979[12], Lings. 1982[13], Sabapathy and Tomenson, 1992[14], Senanayake et al., 1993[15], Swan, 1969[16])***. All studies, irrespective of the affiliation of the authors or their source of funding, agree on the following: under the normal, typical use conditions prevailing in developing countries there is no evidence from medical examinations, chest radiography, spirometry or gas transfer measurements, that paraquat causes any long-term health effects. Two investigations ***(Castro-Gutierrez, 1997 and Dalvie 1999)*** claim to have found adverse health effects either in symptom reporting or exercise induced oxygen desaturation. However, there are serious methodological concerns over both of these findings, and they contrast with other objective measurements in the same studies showing no adverse health effects. This is further supported by a recent study carried out by Professor Marc Schenker from the Department of Epidemiology and Preventive

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[8] Castro-Gutierrez N, McConnell R, Andersson K, Pacheco-Anton F, and Hogstedt C (1997): Respiratory Symptoms, Spirometry and Chronic Occupational Paraquat Exposure. Scand. J Work Environ. Health 23, 421-427.

[9] Dalvie M A, White N, Raine R, Myers J E, London L, Thompson M, Christiani D C (1999): Long-Term Respiratory Health Effects of the Herbicide, Paraquat, Among Workers in the Western Cape. Occup. Environ. Med. 56, 391 – 396.

[10] Howard J K (1980): Paraquat - A Review of Worker Exposure in Normal Usage. J Soc Occup Med 30 (1) 6-11.

[11] Howard J K, Sabapathy N N, and Whitehead P A (1981): A Study of the Health of Malayan Plantation Workers with Particular Reference to Paraquat Spray-men. Br. J Ind. Med. 38, 110-116 (Submitted as PSR80.001B, in Section IIIA of the dossier, and reviewed in the UK Report on Paraquat, Sept 1996).

[12] Levin P J, Klaff L J, Rose A G and Ferguson A D (1979): Pulmonary Effects of Contact Exposure to Paraquat: A Clinical and Experimental Study. Thorax., 34, 150

[13] Lings S (1982): Pesticide Lung - A Pilot Investigation of Fruit-Growers and Farmers During the Spraying Season. Br J Ind Med 39, 370 – 376.

[14] Sabapathy N N, Tomenson J (1992): Health of Paraquat Spray-men in Banana Plantations in the Philippines – an epidemiology study. Report TMF 4180B, ICI Agrochemicals. (Submitted in Section IIIA of the dossier, and reviewed in the UK Report on Paraquat, Sept 1996)

[15] Senanayake N, Gurunathan G, Hart T B, Amerasingne P, Babquille M, Ellapola S B, Udupitille M and Basanayake V (1993): An Epidemiological Study of the Health of Sri Lankan Tea Plantation Workers Associated with Long Term Exposure to Paraquat. Br. J Ind. Med. 50, 257-263

[16] Swan A A B (1969): Exposure of Spray Operators to Paraquat. Br. J Ind. Med. 26, 322-329

Medicine at the University of California in Davis who conducted a state-of-the-art investigation in 338 Costa Rican paraquat handlers and non-handlers from banana, coffee and palm oil farms.

In a recent study ***(Schenker et al, 2004[17])*** all workers underwent pulmonary function testing in the field consisting of spirometry and diffusion capacity. Subjects 40 years of age and younger completed a cardiopulmonary exercise test on a cycle ergometer with measurement of peak oxygen uptake, peak oxygen desaturation and other cardiopulmonary exercise measures. Overall, the study concluded that long-term, low-level paraquat exposure was not associated with clinically significant interstitial lung disease

Conclusion: The extensive published database demonstrates that long-term continuous use of paraquat by workers does not result in long term health effects in man.

These health monitoring studies also provide further reassurance over the application of paraquat-containing products by tractor-mounted sprayers. Knapsack application presents a higher potential for operator exposure. Thus the existing health monitoring studies cover the uses considered in terms of the potential for health effects.

IIIA 7.4 Bystander Exposure

IIIA 7.4.1 Estimation of bystander exposure

Bystander exposure will result primarily from drift. The potential routes of exposure for bystanders are via dermal and inhalation exposure. Such exposure is likely to be brief and not occurring repeatedly to the same individual. The AOEL is therefore considered to be a very conservative toxicological reference value. For the following assessment it is assumed that the person is located at the edge of the field, at a distance of 10 m to the application. The person is assumed to wear some clothing (T-shirt and trousers), which provides some protection to the covered body parts. Exposure is calculated to the non-covered body areas (face, neck front and back, lower arms, hands, feet). Exposure to an incidental bystander is calculated based on the following parameters:

Table IIIA 7.4.1–1 Parameters used for Estimation of Bystander Exposure

		Paraquat
Application rate [mg/m^2]	AR	100
Spray concentration [mg/mL]	C	3.33
Drift at a distance of 10 m [%]	D	0.29% (90%-ile for arable crops)[18]
Exposed body surface [m^2]	BS	0.4250 m^2 (corresponds to the unprotected surface of an adult wearing a T-shirt and trousers)[19]
Dermal absorption [%]	DA	0.323

[17] Schenker MB, Stoecklin M, Lee K, Lupercio R, Zeballos RJ, Enright P, Hennessy T, Beckett LA (2004): Pulmonary function and exercise-associated changes with chronic low-level paraquat exposure. Am J Respir Crit Care Med. 170(7):773-9

[18] Ganzelmeier *et al.*: Studies on the spray drift of plant protection products. Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, Heft 305, 1995.
Updated: BBA (2000:1). Bekanntmachung über Abdriftwerte, die bei der Prüfung und Zulassung von Pflanzenschutzmitteln harangezogen werden. Bundesanzeiger Nr. 100, 26 Mai 2000, 9879-9881.

[19] US EPA (1996). OPPTS Occupational and Residential Exposure Test Guidelines. Series 875

		Paraquat
Application rate [mg/m^2]	AR	100
Body weight [kg]	BW	50 kg
Inhalation exposure [mL/hr]	IE	0.03 ml spray /hr (90%-ile for arable crops)[20] (based on 0.03 mL spray/m^3 and a breathing rate of 1 m^3/hr), conservative approach since spray volume and droplet sizes are larger than for standard applications with downward directed spraying.
Duration of exposure [min]	T	5 min

Dermal exposure calculates as follows:

$$Dermal\ Exposure\ [mg / kg\ bw / day] = \frac{AR \times D \times BS}{BW}$$

Inhalation exposure calculates as follows:

$$Inhalation\ Exposure\ [mg / kg\ bw / day] = \frac{C \times IE \times T}{BW \times 60}$$

Total systemic exposure calculates as follows:

$$Total\ Systemic\ Exposure\ [mg / kg\ bw / day] = Dermal\ Exposure \times DA + Inhalation\ Exposure$$

Based on this approach, total systemic exposure for an incidental bystander calculates as follows:

Table IIIA 7.4.1–2: Estimated bystander exposure values for paraquat, % of the AOEL and risk quotients – tractor mounted boom sprayer and also assumed for hand held application with downward directed spraying.

	Exposure (mg/kg bw/day)	% of AOEL (0.0005 mg/kg bw/day)	RQ*
Dermal exposure	0.002465		
Inhalation exposure	0.000167		
Total systemic exposure	**0.000175**	**34.93**	**0.3493**

*) RQ < 1.0 is acceptable

The applied approach provides a conservative assessment of the exposure risk for incidental bystanders. The calculated exposure level for A3879FA is significantly below the AOEL.

Conclusion: There is no undue risk to bystanders following proposed use of A3879FA.

IIIA 7.4.2 Measurement of bystander exposure

No study has been performed as the calculated exposure level for A3879FA is significantly below the AOEL.

[20] Lloyd G.A. & Bell G.J. (1983). Hydraulic nozzles: Comparative spray drift study. AHU report no. 122

IIIA 7.5 Worker Exposure

IIIA 7.5.1 Estimation of worker exposure assuming personal protective equipment is not used

A3879FA is applied in crops that may require re-entry activities shortly after application. This applies mainly to the perennial crops. However the target of application is the weeds, which grow in between the crops. As discussed previously, as paraquat is a non-selective herbicide, contamination of the crop is strictly avoided. So the dislodgeable foliar residues, which present the potential source of re-entry exposure are limited to the feet and the lower legs of the worker.

To assess the re-entry exposure, the generic re-entry exposure model approved for use in Germany has been used to provide a conservative estimate of exposure during the conduct of re-entry work activities[21].

Parameters for the calculation of exposure are:

Generic DFR value:	1 µg/cm^2 per kg as/ha (under the conservative assumption that DFR do not degrade during the time after application until re-entry)
Transfer Coefficient (TC):	500 cm^2/hour In the absence of specific transfer coefficients the German re-entry exposure model uses the value of 30 000 cm^2/hour which is a worst case figure for activities with very intensive contact to treated crops. For activities of less intensive contacts to foliar residues the model recommends the use of a lower TC. Based on the specific use pattern of paraquat, which is addressed in the first paragraph of this chapter (7.2.3.1), it is considered as adequate to use this lower TC. For the present assessment a TC of 500 has been used. This TC is proposed by EPA[22], for "mowing turf" assuming exposure to feet and lower legs
Time of exposure (A):	8 hours
Clothing penetration (P):	0.05 (5%)
Application rate (R):	1 kg a.i./ha
Bodyweight (W):	60 kg
Dermal absorption (DA):	0.323%

The dermally absorbed dose is calculated as follows: ¨

$$\text{Dermally absorbed dose } [(\text{with clothing})] = \text{DFR x TC x A x R x DA}[(\text{xP})]$$

The calculations of re-entry worker exposure are summarised in Table IIIA 7.5.1-1.

Table IIIA 7.5.1-1: Absorbed doses of paraquat by re-entry workers

Use of PPE	Absorbed Dose (mg/kg bw/day)	% of AOEL (0.0005 mg/kg bw/day)	Risk Quotient
No specific PPE	0.00022	43.1	0.43

The calculated exposure levels are below the AOEL even without specific protective equipment (i.e. the use of closed shoes).

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[21] Krebs B. *et al.*, (1998) Uniform Principles for Safeguarding the Health of Worker Re-entering Crop Growing Areas after Application of Plant Protection Products. Bulletin of the German Plant Protection Service.

[22] Policy Scienence Advisory Council for Exposure, Policy number 003.1, Regarding Agricultural Transfer coefficients, Date May 7, 1998; Revised 7 August 2000, Contacts: J. Evans, J.Dawson, J. Becker.

IIIA 7.5.2 Estimation of worker exposure assuming personal protective equipment is used

Exposure estimates based on no specific PPE result in exposure levels within the AOEL. Therefore no higher TIER approach is required.

IIIA 7.5.3 Estimation of worker exposure assuming personal protective equipment is used and using dislodgeable residues data

Exposure estimates based on no specific PPE result in exposure levels within the AOEL. Therefore no higher TIER approach is required.

IIIA 7.5.4 Measurement of worker exposure

In response to questions raised within the EU Review process, Syngenta provided a worker re-entry biological monitoring study (**Findlay, Iwota, 1995**). This study is reviewed in the **Addendum to the Draft Report for Paraquat (monograph) May 2000.**

The study, conducted in the USA, involves re-entry into cotton crops following the use of paraquat as a desiccant. It was noted in the **Addendum to the Draft Report for Paraquat (monograph) May 2000** that desiccant uses were not supported in the EU review programme and that uses supported in the EU involve application for weed control under circumstances were there is little need for re-entry or inspection of treated crops. It was therefore accepted that the study could be considered to represent a worse case assessment of dermal exposure for workers inspecting a paraquat treated crop.

Paraquat was not detected in any samples for workers re-entering 24 hours post application and was only detected in a single sample from those entering the crop 4 hours after application. The absorbed dose of paraquat for this worker was 0.00004 mg/kg bw/day which is 8% of the (short-term) AOEL.

Although all workers wore long trousers and some wore long sleeved shirts, the potential for dermal contact with treated foliage was reasonably high owing to the height of the crop, which often exceeded the height of the workers. Worker behaviour also indicates frequent hand to face contact as workers wiped away perspiration.

Conclusion: These data show worker exposure to paraquat would be within the AOEL and support a 24 hour re-entry period for workers.

IIIA 7.6 Dermal Absorption

IIIA 7.6.1 *In vivo* in the rat

IIIA 7.6.2 *In vitro*, comparative rat and human studies

Report:	IIIA7.6.2/01 Johnson I (2005). Paraquat 200g/l SL Formulation (A3879FA): *In Vitro* Absorption Of Paraquat Through Human Epidermis. Central Toxicology Laboratory; Syngenta Unpublished Report No: CTL/JV1868/REGULATORY/REPORT. Dates of experimental work: 4 July 2005 to 27 July 2005. (Syngenta File No.PP148/2508).
Guidelines:	OECD Test Guideline No 428 (2004) Skin Absorption: *In vitro* method
Deviations:	None
GLP:	Yes (laboratory certified by the UK authority)

Materials and methods: Paraquat 200g/l SL Formulation; actual paraquat content 202g/l; A3879FA; Batch reference SMU5EP001.

Test System: Human abdominal whole skin (dermis plus epidermis) was obtained *post mortem* from subjects of varying ages. Sheets of epidermis were separated from the dermis following immersion of whole skin in water at 60°C for 40-45 seconds.

Absorption measurements were done using glass diffusion cells in which the epidermal sheet forms a horizontal membrane, with distilled water as a receptor fluid. Throughout the experiment the receptor fluid was stirred and maintained at 32°C by use of a water bath.

The dermal absorption was studied for the undiluted formulation concentrate applied at 10 µl/cm^2 and as a 1/100v/v (nominal 2 g/l) aqueous dilution, also applied at 10 µl/cm^2. All applications remained unoccluded for the duration of the exposure period.

The total exposure period was 24h. The receptor fluid was sampled at intervals throughout the entire 24h exposure period, following the application of the test substance to the outer surface of the skin. After the 24h sample had been taken, the membranes were decontaminated by gently swabbing the surface of the skin and the inside of the donor chamber with a series of natural sponges (approximately 1cm^3) pre-wetted with 3% Teepol®, followed by 2 sponges pre wetted with water to remove any residual Teepol®. The sponges were digested in Soluene 350® and made up to a recorded volume. The epidermal membranes were also dissolved in Soluene 350®. An aliquot of recorded volume of the digests were taken for analysis for inclusion in mass balance and distribution determinations. All samples were analysed by liquid scintillation counting.

Findings:
Concentrate formulation
Absorption of paraquat through human epidermis was very slow with an absorption rate of 0.059µg/cm²/h during the 24 hour exposure period. The total amount of paraquat absorbed over 24 hours was 1.55µg/cm^2 (0.075%).

The vast majority of the applied paraquat (mean 93.5%) was washed off the skin. A small proportion of the dose applied was recovered from the *stratum corneum* (0.027%) and 0.142% was found in the remaining epidermis.

1/100 v/v spray strength dilution
Absorption of paraquat through human epidermis was extremely slow with an absorption rate of 0.002µg/cm²/h during the 24 hour exposure period. The total amount of paraquat absorbed over 24 hours was 0.069µg/cm^2 (0.323%).

The vast majority of the applied paraquat (mean 88.9%) was removed by the skin washing procedure at 24h. A small proportion of the dose applied was recovered from the *stratum corneum* (0.180%) and 0.349% was found in the remaining epidermis.

Conclusion: The results obtained in this study indicate that the absorption of paraquat from a 200 g/l SL formulation concentrate and the 1/100v/v dilution through human epidermis is very slow. These data predict that the dermal absorption of paraquat from potential exposure to this A3879FA formulation would be minimal.

The vast majority of the paraquat applied is likely to be removed from the surface of human skin by normal washing procedures for both concentrate and the spray dilution.

The small residual amounts of paraquat found in human skin, especially that recovered from the *stratum corneum*, is most likely to be lost by desquamation *in vivo*.

These data predict that the dermal absorption of paraquat from potential exposure to this formulation would be minimal. The worse case 24 hour dermal absorptions of 0.075% for concentrate and 0.323% for spray strength have been used in this risk assessment.

Table IIIA 7.6.2-1 - Summary of Paraquat Absorption through Human Epidermis

DETAILS OF APPLICATION OF TEST MATERIALS	MEAN ABSORPTION RATES		MEAN AMOUNT AND PERCENTAGE OF DOSE ABSORBED		
	Time period (h)	Absorption rate (µg/cm²/h ± SEM)	Time (h)	Amount (µg/cm²)	Percent absorbed
Concentrate Formulation	0-8	0.067 ± 0.007			
(203g paraquat/l)			6	0.474	0.023
10µl/cm² (2030µg ai/cm²)	8-24	0.060 ± 0.013	8	0.574	0.028
Unoccluded			10	0.671	0.033
Exposure period 24h	0-24	0.059 ± 0.011	24	1.52	0.075
n = 4					
1/100 aqueous spray dilution	0-8	0.005 ± 0.001			
(21.2g paraquat/l)			6	0.052	0.246
10µl/cm² (2.12µg ai/cm²)	8-24	0.001 ± 0.000	8	0.054	0.256
Unoccluded			10	0.057	0.267
Exposure period 24h	0-24	0.002 ± 0.000	24	0.069	0.323
n = 6					

Table IIIA 7.6.2-2: Summary of Paraquat Distribution in Human Epidermis at 24h. – mean percentage of dose applied

	Concentrate	1:100 Spray Dilution
Donor chamber	0.028	0.630
Wash	93.3	88.9
Tape strips	0.027	0.180
Epidermis	0.142	0.349
Absorbed	0.075	0.323
Total	93.5	90.4

Report:	IIIA7.6.2/02 Owen HM (2003), Paraquat 200g/l SL Formulation (A-3879 BV): *In Vitro* Absorption Of Paraquat Through Human Epidermis. Central Toxicology Laboratory, Syngenta Unpublished Report No. CTL/JV1748/REGULATORY/REPORT, study dates June 2003. Syngenta File No. PP148/1858
Guidelines:	OECD (2000). Test Guideline 428: Skin Absorption: *In Vitro* Method.
Deviations:	None. The study met all criteria specified in the draft guideline referenced above.
GLP:	Yes (laboratory certified by the UK authority).

Materials and methods: Paraquat 200g/l SL formulation (A-3879 BV); Batch No. J6283/109;

Findings:

Concentrate formulation A-3879 BV
Absorption of paraquat from the concentrate formulation through human epidermis was very slow giving an absorption rate of 0.108µg/cm²/h during the 24 hour exposure period. The absorption was slowest during the first 6 hours of exposure (0.066µg/cm²/h) and the greatest absorption occurred during the 6 to 24h exposure period (0.131µg/cm²/h). The amount of paraquat absorbed at 24 hours was 2.77µg/cm^2 (0.136%).

The vast majority of the applied paraquat (mean 91.8%) was washed off the skin. A small proportion of the dose applied was recovered from the *stratum corneum* (0.027%) and 0.236% was found in the remaining epidermis.

1:100 v/v spray strength dilution
Absorption of paraquat from the 1:100 spray dilution through human epidermis was extremely slow giving an absorption rate of 0.003µg/cm²/h during the 24 hour exposure period. The absorption was fastest during the first 6 hours of exposure (0.005µg/cm²/h) and slowed to 0.003µg/cm²/h during the 6 to 24h exposure period. The amount of paraquat absorbed at 24 hours was 0.079µg/cm^2 (0.374%).

The vast majority of the applied paraquat (mean 90.3%) was washed off the skin. A small proportion of the dose applied was recovered from the *stratum corneum* (0.298%) and 3.18% was found in the remaining epidermis.

Table IIIA 7.6.3-3: Summary of Paraquat Absorption Through Human Epidermis From The Concentrate Formulation (A-3879 BV) and 1:100v/v Spray Dilution (number of samples = 5 (conc) and 4 (spray); duration of exposure = 24 hours)

DETAILS OF APPLICATION OF TEST MATERIALS	MEAN ABSORPTION RATES		MEAN AMOUNT AND PERCENT OF DOSE ABSORBED		
	Time period (h)	Absorption rate ($\mu g/cm^2/h \pm$ SEM)	Time (h)	Amount ($\mu g/cm^2$)	Percent absorbed
Concentrate formulation	0-6h	0.066 ± 0.018	6	0.427	0.021
10µl/cm² (2038µg ai/cm²)	6-24h	0.131 ± 0.042	8	0.570	0.028
unoccluded	0-24h	0.108 ± 0.034	10	0.721	0.035
			24	2.77	0.136
1:100v/v spray dilution	0-6h	0.005 ± 0.001	6	0.031	0.148
10µl/cm² (21.2µg ai/cm²)	6-24h	0.003 ± 0.001	8	0.038	0.177
unoccluded	0-24h	0.003 ± 0.001	10	0.043	0.203
			24	0.079	0.374

Table IIIA 7.6.3-4 Summary of Paraquat Distribution In Human Epidermis At 24h. Percent of dose applied

	Concentrate (A-3879 BV)	1:100 Spray Dilution
Spreaders	1.70	0.134
Donor chamber	4.31	9.04
Wash	91.8	90.3
Tape strips	0.027	0.298
Epidermis	0.236	3.18
Absorbed	0.136	0.374
Total	98.2	103

Conclusion: These data predict that the dermal absorption of paraquat from potential exposure to this SL formulation would be minimal. The worst case 24 hour dermal absorption values are 0.136 % for concentrate and 0.374% for spray strength.

Comparative percutaneous absorption of paraquat from 2 INTEON formulations A3879FA and A-3879 BV through human skin in vitro.

A3879FA is similar in composition to A-3879 BV. Both are 200g/l formulations although the adjuvant loading in A3879FA is lower than A-3879 BV (as described in Document J). Because adjuvants can generally enhance skin absorption and A3879FA may be tank mixed with other adjuvants, the percutaneous absorption of A3879FA is compared below to that of adjuvant containing A-3879 BV. The table shows that the percutaneous absorption of paraquat with 200 g/l A-3879 BV was not significantly altered by the increased level of adjuvants in the formulation and is still very low and consistent with the *in vivo* human percutaneous absorption values of less than 0.3% published by Wester et al 1984[23]. Therefore values from the study with A3879FA are used for risk assessment.

Table IIIA 7.6.3-5: Comparison of the percutaneous absorption in vitro of A3879FA (low adjuvant loading) vs A-3879BV (with adjuvant)

	Penetration rates µg/cm²/h (mean ± S.E.M)	Time	Percent absorbed (mean)
A3879FA Concentrate			
0-8 hours	0.067 ± 0.007	6	0.023
8-24 hours	0.060 ± 0.013	8	0.028
0-24 hours	0.059 ± 0.011	24	0.075
A-3789 BV Concentrate			
0-6 hours	0.066± 0.018	6	0.021
6-24 hours	0.131±0.042	8	0.028
0-24 hours	0.108±0.034	24	0.136
A3879FA 1/100 aqueous dilution			
0-8 hours	0.005 ± 0.001	6	0.246
8-24 hours	0.001 ± 0.000	8	0.256
0-24 hours	0.002 ± 0.000	24	0.323
A-3879 BV 1/100 aqueous dilution			
0-6 hours	0.005±0.001	6	0.148
6-24 hours	0.003±0.001	8	0.177
0-24 hours	0.003±0.001	24	0.374

[23] Wester RC, Maibach HI, Bucks CA and Aufrere (1984) In vivo percutaneous absorption of paraquat from hand, leg and forearm of humans. .Journal of Toxicology and Environmental Health 16, 25-37

IIIA 7.7 Dislodgeable Residues

IIIA 7.7.1 Foliar

This is not an EC data requirement

IIIA 7.7.2 Soil

This is not an EC data requirement

IIIA 7.7.3 Indoor surface re-volatilization

This is not an EC data requirement

IIIA 7.8 Epidemiology

This is not an EC data requirement

IIIA 7.9 Data on Formulants

IIIA 7.9.1 Material safety data sheets for each formulant

CONFIDENTIAL information - data provided separately (Document J)

IIIA 7.9.2 Available toxicological data for each formulant

CONFIDENTIAL information - data provided separately (Document J)

IIIA 7.10 Domestic Animal/Livestock Safety

This is not an EC data requirement

IIIA 7.11 Other/Special Studies

This is not an EC data requirement

Appendix 1: Exposure Estimates

Table IIIA 7.2.1.1.–2: German Model, Tractor mounted boom sprayer in high crops, 20 ha/day, 1 kg a.i./ha

A. Model Data:		
Exposure: mixing/loading per kg a.i. handled:	2.4	mg on hands
	0.0006	mg by inhalation
Exposure: spray operation per kg a.i. handled:	0.06	mg on head
	0.38	mg on hands
	1.6	mg/on body surface
	0.001	mg/by inhalation

B. Estimated Exposure Without and With Protective Clothing (mg)				
Exposed Body Parts	**Shorts, short sleeved shirt**	**Personal protective equipment**		
Mixing/loading:	**Paraquat**	*penetration factor:*		**Paraquat**
Hands	48	gloves	***0.01***	0.48
inhalation	0.012	no mask	***1***	0.012
Spraying:				
Hands:	7.6	no gloves	***1***	7.6
Head:	1.2	hat	***0.5***	0.6
Body:	32	coverall	***0.05***	1.6
inhalation	0.02	no mask	***1***	0.02
Total dermal :	**88.8**			**10.28**
Total inhalatory:	**0.032**			**0.032**

E. Systemic Exposure	**Paraquat**	**Paraquat**
Mixing/loading		
dermal exposure	48.00	0.48
absorption	0.075%	0.075%
absorbed dose	0.0360	0.000360
inhalation	0.012	0.012
absorption	100%	100%
absorbed dose	0.0120	0.0120
total absorbed mix/load	0.0480	0.0124
Spraying		
dermal exposure	40.8	9.8
absorption	0.32%	0.32%
absorbed dose	0.1318	0.0317
inhalation	0.02	0.02
absorption	100%	100%
absorbed dose	0.020	0.020
total absorbed spraying	0.152	0.052
Total absorbed (mg/person)	0.200	0.064
Total absorbed (mg/kg b.w.)	**0.0029**	**0.0009**
AOEL (mg/kg b.w.)	0.0005	0.0005
% of AOEL	**570.81**	**182.90**
Risk Quotient	**5.71**	**1.83**

Table IIIA 7.2.1.1.–3: German Model, Tractor mounted boom sprayer in high crops, 20 ha/day, 1 kg a.i./ha , using additionally respiratory mask during mixing/loading and gloves also during application (always when direct contact to contaminated surfaces) is possible

Section A as above

B. Estimated Exposure Without and With Protective Clothing (mg)				
Exposed Body Parts	**Shorts, short sleeved shirt**	**Personal protective equipment**		
Mixing/loading:		*penetration factor:*		**Paraquat**
Hands		gloves	***0.01***	0.48
inhalation		mask	***0.05***	0.0006
Spraying:				
Hands:		gloves	***0.01***	0.076
Head:		hat	***0.5***	0.6
Body:		coverall	***0.05***	1.6
inhalation		no mask	*1*	0.02
Total dermal :				**2.756**
Total inhalatory:				**0.0206**
E. Systemic Exposure				**Paraquat**
Mixing/loading				
dermal exposure				0.48
absorption				0.075%
absorbed dose				0.000360
inhalation				0.001
absorption				100%
absorbed dose				0.0006
total absorbed mix/load				0.0010
Spraying				
dermal exposure				2.276
absorption				0.32%
absorbed dose				0.0074
inhalation				0.02
absorption				100%
absorbed dose				0.020
total absorbed spraying				0.027
Total absorbed (mg/person)				0.028
Total absorbed (mg/kg b.w.)				**0.0004**
AOEL (mg/kg b.w.)				0.0005
% of AOEL				**80.89**
Risk Quotient				**0.81**

Table 7.2.1.1.–4: UK-POEM, Tractor mounted boom sprayer in field crops, 50 ha/day, 1 kg a.i./ha, 5 L container, 300 l spray volume

A. PRODUCT DATA					
1. Product name	A 3879 FA				
2a. Active ingredient	paraquat				
2b. Concentration	200	mg/ml			
3. Formulation type	SL				
4a. Main solvent					
4b. Concentration of solvent	na				
5. Maximum in-use ai concentration	3.333	mg/ml			
B. EXPOSURE DURING MIXING AND LOADING					
1a. Container size	5	litres			
1b. Hand contamination/operation	0.01	ml			
2. Application dose	5.00	litres product/ha	50	kg ai/day	
3. Work rate	50	ha/day			
4. Number of operations	50	/day			
5. Hand contamination	0.5	ml/day			
6. Protective clothing	**NONE**		**GLOVES**		
7. Transmission to skin	100		10	%	
8. Dermal exposure to formulation	0.5		0.05	ml/day	
9. Concentration of ai	200		200	mg/ml	
10. Dermal exposure to ai	100.000		10.000	mg/day	
11. Percent absorbed	0.075		0.075	%	
12. Absorbed dose	**0.00125**		**0.00013**	mg/kg bw/day	

C. EXPOSURE DURING SPRAY APPLICATION					
1. Application technique - Vehicle with cab boom hydraulic nozzles					
2. Application volume	300	spray/ha			
3. Volume of surface contamination	10	ml/h			
4. Distribution	Hands	Hands	Trunk	Legs	
	65	65	10	25	%
5. Clothing	NONE	GLOVES	PERMEABLE	PERMEABLE	
6. Penetration	100	10	5	15	%
7. Dermal exposure	6.5	0.65	0.05	0.375	ml/h
8. Duration of exposure	6	h			

PPE	**NONE**	**GLOVES**	
9. Total dermal exposure to spray	41.55	6.45	ml/day
10. Concentration of ai	3.333	3.333	mg/ml
3. Dermal exposure to ai	138.500	21.500	mg/day
11. Percent absorbed	0.323	0.323	%
12. Absorbed dose	**0.00746**	**0.001**	**mg/kg bw/day**

E. INHALED EXPOSURE DURING SPRAY APPLICATION				
1. Inhalation exposure	0.01	ml/h		
2. Duration of exposure	6	h		
3. Concentration of ai	3.333	mg/ml		
4. Inhalational exposure to ai	0.200	mg/day		
5. Percent absorbed	100	%		
6. Absorbed dose	**0.003333**	**mg/kg bw/day**		
F. PREDICTED EXPOSURE			**% of AOEL**	**RQ**
1. No gloves	**0.01204**	**mg/kg bw/day**	**2407.9**	24.079
2. Gloves only when mixing/loading	**0.0109**	**mg/kg bw/day**	**2182.9**	21.829
3. Gloves only during spray application	0.0057	mg/kg bw/day	1148.2	11.482
4. Gloves during spray application & mix/loading	**0.0046**	**mg/kg bw/day**	**923.2**	9.232

Table IIIA 7.2.1.1.–5: UK-POEM, Tractor mounted boom sprayer in field crops, 50 ha/day, 1 kg a.i./ha, 1 L container, assuming the use of coverall, protective gloves and respiratory mask during all operations

Section A and B as above. Correction factors for reduced clothing permeation and efficacy of respiratory protection taken from German model.

C. EXPOSURE DURING SPRAY APPLICATION

1. Application technique	- Vehicle with cab boom hydraulic nozzles					
2. Application volume	300				spray/ha	
3. Volume of surface contamination		10			ml/h	
4. Distribution	Hands		Hands	Trunk	Legs	
	65		65	10	25	%
5. Clothing	NONE		GLOVES	PERMEABLE	PERMEABLE	
6. Penetration	100		10	5	5	%
7. Dermal exposure	6.5		0.65	0.05	0.125	ml/h
8. Duration of exposure		6	h			
PPE	**NONE**		**GLOVES**			
9. Total dermal exposure to spray	40.05		4.95	ml/day		
10. Concentration of ai	3.333		3.333	mg/ml		
3. Dermal exposure to ai	133.500		16.500	mg/day		
11. Percent absorbed	0.323		0.323	%		
12. Absorbed dose	**0.00719**		**0.0009**	**mg/kg bw/day**		

E. INHALED EXPOSURE DURING SPRAY APPLICATION

1. Inhalation exposure	0.01	ml/h	
2. Duration of exposure	6	h	
3. Concentration of ai	3.333	mg/ml	
4. Inhalational exposure to ai	0.200	mg/day	
5. Percent absorbed	100	%	
6. Absorbed dose	**0.003333**	**mg/kg bw/day**	

Respiratory protection (95% reduction)	**0.01**	
	100	**%**
	0.00016667	**mg/kg b.w./day**

F. PREDICTED EXPOSURE

			% of AOEL	RQ
1. No gloves	0.011770	mg/kg bw/day	2354.0	24.079
2. Gloves only when mixing/loading	0.0106	mg/kg bw/day	2129.0	21.829
3. Gloves only during spray application	0.0055	mg/kg bw/day	1094.3	11.482
4. Gloves during spray application & mix/loading	0.0043	mg/kg bw/day	869.3	9.232
5.Gloves coverall and respiratory mask during all operation	**0.00118**	**mg/kg bw/day**	**236.0**	**2.360**

Table IIIA 7.2.1.1.–6 UK-POEM, knapsack application, 1 kg a.i./ha, 300 L spray volume, 5 L bottles; 1 ha/day

A. PRODUCT DATA					
1. Product name	A 3879 FA				
2a. Active ingredient	paraquat				
2b. Concentration	200	mg/ml			
3. Formulation type	SL				
4a. Main solvent					
4b. Concentration of solvent	NA				
5. Maximum in-use ai concentration	3.333	mg/ml			
B. EXPOSURE DURING MIXING AND LOADING					
1a. Container size	5	litres			
1b. Hand contamination/operation	0.01	ml			
2. Application dose	5	litres product/ha	1	kg ai/day	
3. Work rate	1	ha/day			
4. Number of operations	20	/day			
5. Hand contamination	0.2	ml/day			
6. Protective clothing	**NONE**		**GLOVES**		
7. Transmission to skin	100		10	%	
8. Dermal exposure to formulation	0.2		0.02	ml/day	
9. Concentration of ai	200		200	mg/ml	
10. Dermal exposure to ai	40.000		4.000	mg/day	
11. Percent absorbed	0.075		0.075	%	
12. Absorbed dose	**0.001**		**0.0001**	mg/kg bw/day	

C. EXPOSURE DURING SPRAY APPLICATION					
1. Application technique - Knapsack hydraulic nozzles low level outdoor					
2. Application volume	300	spray/ha			
3. Volume of surface contamination	50	ml/h			
4. Distribution	Hands	Hands	Trunk	Legs	
	25	25	25	50	%
5. Clothing	NONE	GLOVES	permeable	permeable	
6. Penetration	100	10	20	18	%
7. Dermal exposure	10	1.25	2.5	4.5	ml/h
8. Duration of exposure	6	h			
PPE	**NONE**	**GLOVES**			
9. Total dermal exposure to spray	102	49.5	ml/day		
10. Concentration of ai	3.333	3.333	mg/ml		
3. Dermal exposure to ai	340.000	165.000	mg/day		
11. Percent absorbed	0.323	0.323	%		
12. Absorbed dose	**0.018**	**0.009**	**mg/kg bw/day**		

E. INHALED EXPOSURE DURING SPRAY APPLICATION				
1. Inhalation exposure	0.02	ml/h		
2. Duration of exposure	6	h		
3. Concentration of ai	3.333	mg/ml		
4. Inhalational exposure to ai	0.400	mg/day		
5. Percent absorbed	100	%		
6. Absorbed dose	**0.007**	**mg/kg bw/day**		
F. PREDICTED EXPOSURE			%AOEL	RQ
1. No gloves	0.025	mg/kg bw/day	5094.0	50.94
2. Gloves only when mixing/loading	0.025	mg/kg bw/day	5004.0	50.04
3. Gloves only during spray application	0.016	mg/kg bw/day	3209.8	32.10
4. Gloves during spray application & mix/loading	0.016	mg/kg bw/day	3119.8	31.20

Table IIIA 7.2.1.1– 7: UK-POEM, knapsack application, 1 kg a.i./ha, 300 L spray volume, 5 L bottles; 1 ha/day

Section A and B as above. Correction factors for reduced clothing permeation and efficacy of respiratory protection taken from German model.

C. EXPOSURE DURING SPRAY APPLICATION						
1. Application technique - Knapsack hydraulic nozzles low level outdoor						
2. Application volume	300		spray/ha			
3. Volume of surface contamination		50	ml/h			
4. Distribution	Hands		Hands	Trunk	Legs	
	25		25	25	50	%
5. Clothing	NONE		GLOVES	permeable	permeable	
6. Penetration	100		10	5	5	%
7. Dermal exposure	10		1.25	0.625	1.25	ml/h
8. Duration of exposure		6	h			
PPE	**NONE**		**GLOVES**			
9. Total dermal exposure to spray	71.25		18.75	ml/day		
10. Concentration of ai	3.333		3.333	mg/ml		
3. Dermal exposure to ai	237.500		62.500	mg/day		
11. Percent absorbed	0.323		0.323	%		
12. Absorbed dose	**0.013**		**0.003**	**mg/kg bw/day**		
E. INHALED EXPOSURE DURING SPRAY APPLICATION						
1. Inhalation exposure	0.02	ml/h				
2. Duration of exposure	6	h				
3. Concentration of ai	3.333	mg/ml				
4. Inhalational exposure to ai	0.400	mg/day				
5. Percent absorbed	100	%				
6. Absorbed dose	**0.007**	**mg/kg bw/d**				

Respiratory protection (95% reduction)	**0.02**	
	100	**%**
	0.0003	**mg/kg bw/d**

F. PREDICTED EXPOSURE			Percent account of established AOEL	
1. No gloves	0.020	mg/kg bw/day	3990.4	39.904
2. Gloves only when mixing/loading	0.020	mg/kg bw/day	3900.4	39.004
3. Gloves only during spray application	0.011	mg/kg bw/day	2106.3	21.063
4. Gloves during spray application & mix/loading	0.010	mg/kg bw/day	2016.3	20.163
5.Gloves and respiratory mask during all operations ae	**0.00375**	**mg/kg bw/day**	**749.6**	**7.496**

Appendix 2: Exposure Studies

These studies were submitted during the EU process but are summarized below for convenience.

Tractor application of GRAMOXONE® Extra

Meier DJ (1995). "Paraquat: Worker Exposure During Mixing, Loading And Application Of Gramoxone® Extra To Pecans Using Vehicle-Mounted, Groundbom Equipment. Zeneca Ag Products Western Research Center, Unpublished Report No. RR 95-019B. 28.04.1995

Objectives

The main objective of this study was to determine the systemic absorption of paraquat by mixer-loader-applicators using tractor-mounted sprayers to apply 'Gramoxone' Extra (a 'Soluble Liquid' (SL) formulation containing 300 g paraquat/litre) in pecan orchards in Georgia, USA during 1994.

Table IIIA 7.3.3-5: Application conditions of the operator exposure study with Paraquat

Formulation	300 g/L
Crop	Pecan nuts
Use rate:	1.05 kg a.i./ha
Spray liquid/ha	124-393 L/ha,
Number of replicates	17 operators
Spraying equipment	Tractors without cabins, boom sprayer beside (3) the tractor or at the rear (147), operators distance to the boom 0.9-8.5m.
Protective clothing/Work clothing	Clothing was long pants and short sleeved shirt (14 operators) one operator used long sleeved shirt, 2 operators used Tyvek suits over normal clothing. Only 8 workers wore protective gloves when mixing and loading; one of these workers wore gloves only for the first two mix-loads. One worker wore full protective clothing, i.e. rubber apron, faceshield, 'Tyvek' suit as well as protective gloves when mixing and loading.
Work rate	Average 5.9 hours/day, (4 – 11 hours), Average 12 ha /day (3.2 to 30 ha)

Absorption of paraquat was measured by collecting complete 24-hour urine samples for a 7-day period. This comprised one-day before exposure as a baseline day (workers had no contact with paraquat for 6 days prior to exposure), the exposure day and 5 days afterwards. 24 h urine volumes were measured and two sub-samples prepared of each sample and stored frozen. On completion of the study, one set was transported to the laboratory for analysis, the other set remained in local frozen storage until analysis of the first set was complete.

Analysis was by a radioimmunoassay method for paraquat. For creatinine analysis was conducted using the Jaffe reaction. The limit of quantification was 10 ng paraquat/ml urine. The limit of detection was 5 ng paraquat/ml urine.

Results

Detailed observations on work and hygiene practices indicated that some workers smoked, chewed and drank during the exposure period. There were also incidents of operator contamination from equipment maintenance, tank overflow, handling contaminated equipment and removing secondary seals without gloves.

The 24-hour urine volumes and creatinine concentrations demonstrated completeness of collection by the workers. Paraquat was detected in urine samples from only 6 of the 17 workers and only for the day of exposure. None of the urine samples taken on days 2 and 3 contained

detectable amounts of paraquat (limit of detection - 5 ng/ml) and it was therefore considered unnecessary to analyse samples from days 4 and 5. The fact that paraquat was not detected in the urine samples taken from these operators on the days following exposure demonstrates that paraquat is rapidly excreted. The amounts of paraquat absorbed were calculated from the amount excreted in urine following correction for the percentage of a parenteral dose excreted in the urine of monkeys (59%, Wester, et al., 1984[24]).

For the 6 out of 17 workers who absorbed detectable amounts of paraquat, the mean exposure was 0.21 µg/kg bw/day (range 0.07 to 0.44 µg/kg/day). The highest exposure was for a worker who was noted to have handled the product particularly carelessly and did not wear any protective gloves or other protective clothing during mixing and loading.

For risk assessment purposes it is appropriate to separate the 17 workers into two groups according to whether they complied with the label recommendation to wear protective equipment or not; in particular, whether the workers wore protective gloves. As stated above, 9 workers did not wear gloves during mixing and loading. It is evident from the data that measurable paraquat was detected only in workers within this sub-group and not in any worker who complied with the product label requirement to wear protective gloves.

An estimate of the absorbed dose for risk assessment for the protected workers can be obtained by taking account of the mean daily urine volume of 1635 ml and a value equivalent to one half the limit of detection of 0.005 µg/ml, which is 0.0025 µg/ml:

$$0.0025\ \mu g/ml \times 1635ml = 4.087\ \mu g \text{ paraquat excreted}.$$

Wester *et al* (1984) showed that 59% of a parenteral dose of paraquat was excreted in the urine of monkeys. This fact can be used to estimate the absorbed dose of paraquat:

$$4.087\ \mu g \times \frac{100}{59} = 6.96\ \mu g \text{ paraquat absorbed}$$

The mean body weight of these workers was 97 kg:

Estimated absorbed dose of paraquat = **(0.0714 µg/kg/day) = 0.000071mg/kg/day**

Using a similar type of calculation for the data of the unprotected workers, because paraquat was measured in the urine of 6 out of 9 of them, it is appropriate to calculate the mean and range of absorbed doses: A value equivalent to one half the limit of detection was included for the 3 individuals with none detected.

Mean absorbed dose of paraquat: = **0.00015 (0.000044 to 0.00044) mg/kg/day**

Chester, et. Al (1989) "Paraquat: Dermal Exposure of , and Absorption by, Sri Lankan Tea Plantation Workers". ICI Agrochemicals, Unpublished Report No.TMF 3189.

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[24] Referenced in the study report: Wester R C, et al. In vivo percutaneous absorption of paraquat from hand, leg and forearm of humans. J. Tox environ Helath 14: pp 759-762

In this study conducted in tea plantations in Sri Lanka, the exposure to, and the absorption of, paraquat were determined for mixer/loaders and spray operators during typical weed control with hand-held knapsack sprayers over 5 consecutive days of spraying.

Table IIIA 7.3.3-6: Application conditions of the operator exposure study with Paraquat

Formulation	Grammoxone W, (200 g a.i./L)
Crop	Tea
Use rate:	0.7 product L in 450L water/ha (0.31 g a.i./L).
Spray liquid/ha	450 litres/ha
Number of replicates	12 (2 mixer/loaders; 10 spray operators). Operators were working during 5 consecutive days.
Spraying equipment	Mixer loaders made spray solution in drums and poured the spray liquid with buckets into the knapsack sprayers. Hand operated knapsack sprayers. 15 L capacity
Protective clothing/Work clothing	Short-sleeved shirt, shorts no socks no footwear (all operators).
Work rate	About 0.4 ha/day

Absorption of paraquat as measured by daily collecting complete 24-hour urine samples on the day prior to the first application, (baseline) during the 5 days of application and until 8 days after the last application (13 days of collection in total). These samples were analysed for paraquat and creatinine.

Results

There was no measurable absorption of paraquat as indicated by urinary excretion of the compound (the limit of quantification was 0.03 µg/ml) following collection of complete 24 hour samples of urine for 6 days after the last day of spraying. The average amount of paraquat excreted, based on the average urine volume of 1.94 litres and half the limit of quantification of 0.015 µg/ml, was 29 µg/day. It is worth noting that, because workers were monitored during 5 consecutive days of paraquat use, the total number of exposures and therefore replicates was 50 for the applicators (10x 5 days) and 10 for the mixer/loaders of the product (2x 5 days).

The estimated average daily absorption of paraquat over the 5-day period of exposure in the Sri Lankan study was therefore:

$$29\,\mu g/day \times \frac{100*}{59} = 49\,\mu g/day$$

* Based on data of Wester *et al*(1984).

Using the average worker bodyweight of 49 kg this equates to: $\frac{0.49\,\mu g/day}{49\,kg} = 1\,\mu g/kg/day$

At the limit of quantification for this study (0.03 µg/ml) no measurable absorption of paraquat was detectable at this level.

Findlay M L et al.(1998). "Paraquat: Worker Exposure During Mixing, Loading And Application of GramoxoneWith Knapsack Sprayers , Zeneca Agrochemicals, Unpublished Report No. WER 004 09 April 1998.

A study has been undertaken to determine the absorbed dose of paraquat in 20 workers who mixed, loaded and applied 'Gramoxone' with hand held knapsack sprayers for weed control in citrus orchards in Spain during November 1997.

Table IIIA 7.3.3-7: Application conditions of the operator exposure study with Paraquat

Formulation	Gramoxone (aqueous soluble liquid 200 ga.i./L)
Crop	Citrus
Use rate:	600-800 g a.i./ha
Spray liquid/ha	300-400 l
Number of replicates	20
Spraying equipment	Knapsack sprayers with 18 L capacity
Protective clothing/Work clothing	Standardised clothing: long sleeved cotton shirt, long cotton trousers, cotton underpants, cotton socks and rubber boots. Additionally during mixing/loading: gloves, face shield: :
Work rate	12 tank loads in 6 hours

The absorbed dose of paraquat was determined by use of a biological monitoring method. This involved collection of workers' urine for a continuous 7-day period from the day prior to application (baseline day) until 5 days after the day of application followed by analysis for unchanged paraquat. Also creatinine levels were determined. The amounts of paraquat absorbed were calculated from the amount excreted in urine following correction for the percentage of a parenteral dose excreted in the urine of monkeys (59%, Wester, et al., 1984[25]).

Results

Paraquat was detected in the urine of 18 of the 20 workers using a highly sensitive radio-immunoassay method with a limit of quantification of 0.75 ng/ml.

The geometric mean (range) estimated absorbed dose of paraquat was 77 ng/kg/day (<LOQ - 408 ng/kg/day).

The arithmetic mean absorbed dose was 149 ng/kg/day. There was an apparent association between the higher of the absorbed doses of paraquat and the observations on spray solution contamination of clothing involving the backs of the shirts.

[25] Referenced in the study report: Wester R C, et al. In vivo percutaneous absorption of paraquat from hand, leg and forearm of humans. J. Tox environ Helath 14: pp 759-762

Findlay, M.L. Diquat: Worker Exposure During Mixing, Loading and Application of 'Reglone' with Knapsack Sprayers. Zeneca Ag Products Report No. RR-97-004B. 23rd January 1998.

The objectives of this study were to determine the potential dermal and inhalation exposure (passive dosimetry) to and absorption (bioavailability) of diquat by 20 workers involved in the mixing, loading and application of 'Reglone' (an SC formulation containing 200 g diquat per litre) using knapsack sprayers in a banana plantation in Guatemala during 1996.

Table IIIA 7.3.3-8: Application conditions of the operator exposure study with Diquat

Formulation	Reglone (aqueous soluble liquid 200 ga.i./L)
Crop	Banana
Use rate:	600 g a.i./ha
Spray liquid/ha	
Number of replicates	20
Spraying equipment	Knapsack sprayers with 16 L capacity (spot - and broadcast application)
Protective clothing/Work clothing	Standardised clothing: long sleeved cotton shirt, long cotton trousers, cotton socks and rubber boots. Additionally during mixing/loading: gloves, face shield.
Work rate	275 – 323 minutes (Total diquat applied per worker ranged from 2.88 kg to 3.84 kg.)

Potential dermal exposure was measured by a whole body dosimetry method (collection and sectioning of cotton clothing, collection of hand wash water) . Inhalation exposure was measured by Glass fibre filters housed in IOM samplers attached to the collars of the workers' clothing. The samplers were connected to to personal air-sampling pumps

Systemic absorption of diquat was measured by collection of the workers' urine over a 7-day period. Sampling commenced on the day prior to exposure and ceased on the first void of the sixth day following exposure.

Clothing dosimeters and air sampler filters were extracted, cleaned up and analysed for diquat by HPLC. Diquat was extracted from urine using solid phase extraction and converted to the dipyridone derivative, which was then determined by liquid chromatography with fluorescence detection. Creatinine excretion was measured to provide an assessment of compliance in respect to collection of total urine output.

Results

Spraying was a mixture of spot and broadcast application and took place over flat areas of fairly dense plantation, with gullies every 100 metres. Workers sprayed both types of terrain. Whilst spraying the gullies it was often necessary for the lance to be held at chest and/or face height, resulting in many of the workers' clothing becoming contaminated. There were numerous incidents resulting in spray-wet clothing. High temperatures and humidity had a significant effect on the comfort of the operator, with arm to face contact being observed for most workers. One worker (No. 3) experienced contamination due to defective equipment.

Measured creatinine excretion in the study showed that on the days where diquat was detected in samples (days 2 and 3) daily excretion of creatinine was acceptable for most workers, suggesting full collections were made on these critical days. For four workers (4, 5, 6, and 12) there was considerable variability in the daily excretion of creatinine, suggesting that these workers' urine collections were incomplete. However, in the majority of cases where low creatinine excretion

was observed, these samples corresponded to collections made near the end of the study, where any concentrations of diquat present were below the limit of quantification. The non-compliance in collection of total urinary output for certain workers is therefore not considered to have affected the overall estimation of systemic exposure.

The absorbed dose was calculated by adjusting the diquat excreted in workers urine for the percentage of an intravenous dose (61%) excreted in urine . (Feldman and Maibach, 1974[26]).

Diquat was detected in urine samples of all twenty workers. On the pre-exposure day diquat was detected in the sample of Worker 12. This worker's sample contained diquat at just above the limit of quantification (0.71 ng/ml). On the day of application (day 2) diquat was found in urine samples of all workers. In fifteen of the twenty workers diquat was eliminated within 24 hours of applying the product (day 3). No diquat was detected in the urine of any worker after day 3.

Workers 8, 11, 12, 16 and 17 incurred the highest absorbed doses of diquat, with worker 11 having the highest (0.00059 µg/kg bw/day). It is noted that this worker was involved in treatment of canal banks with the spray lance being held at head height.

Workers having the highest potential and systemic exposures did not mix, load or apply the product differently from others participating in the study. All workers demonstrated generally good compliance with hygiene standards during mixing/loading and product application. However, the spraying at chest and/or head height in the gullies caused significant contamination of their clothing.

The mean (range) absorbed dose of diquat was 0.000125 (0.000015 to 0.00059) mg/kg/d.

[26] referenced in the study report: Feldmann, R.J. and Maibach, H.I. Toxicol. and Applied Pharmacol. 28, 126 – 132 (1974)