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Chemical Review Committee
Ninth meeting
Rome, 22–25 October 2013
Item 5 (c) (iv) of the provisional agenda*

Technical work: review of notifications of final regulatory actions: methamidophos

Methamidophos: supporting documentation provided by the European Union

Note by the Secretariat

Addendum

The annex to the present note sets out the documentation provided by the European Union to support its notification of final regulatory action for methamidophos as a pesticide. The documentation has not been formally edited.

* UNEP/FAO/RC/CRC.9/1.

K1352600 130813

Annex

Supporting documentation provided by the European Union on methamidophos

A. Monograph prepared in the context of the inclusion of the following active substance in Annex I of the Council Directive 91/414/EEC: Methamidophos (August 2000)

B. Opinion of the Scientific Panel on Plant health, Plant protection Products and their Residues on a request from the Commission related to the evaluation of methamidophos in toxicology in the context of Council Directive 91/414/EEC (September 2004)

C. Opinion of the Scientific Panel on Plant health, Plant protection products and their Residues on a request from the Commission related to the evaluation of methamidophos in ecotoxicology in the context of Council Directive 91/414/EEC (December 2004)

D. Review report for the active substance methamidophos (March 2006)

E. Commission Directive 2006/131/EC of 11 December 2006 amending Council Directive 91/414/EEC to include methamidophos as an active substance (December 2006)

Ministry of Health
Department of Food, Nutrition, and Veterinary Public Health
Piazza Marconi, 25
I - 00144 ROMA
ITALY

Monograph prepared in the context of the inclusion of the following active substance in Annex I of the Council Directive 91/414/EEC

Methamidophos

Volume 1

Report and Proposed Decision

August 2000

LEVEL 1

Statement of the subject matter and purpose of the monograph

Methamidophos

1.1 Purpose for which the monograph was prepared (Document A)

The dossiers are submitted to support first inclusion of the existing active substance methamidophos in Annex I of Directive 91/414, according to Commission Regulations (EEC) No 3600/92 and 993/94.

1.1.1 Summary and assessment of the steps taken to collectively present the dossier

Two notifiers, i.e. Bayer AG and K&N Efthymiadis SA submitted individual dossiers to support inclusion of Methamidophos in Annex I of Council Directive 91/414/EEC. Bayer AG and Tomen submit a dossier together. Only Bayer/Tomen presented an adequate dossier to support a complete monograph.

Note: in the following monograph letter (a) or (b) before the paragraphs identifies Bayer AG or K&N Efthymiadis SA respectively.

1.2 Identity of the active substance (IIA 1)

1.2.1 Name and address of applicant for inclusion of the active substance in Annex I (IIA 1.1)

Two dossiers were submitted by the following notifiers:

a) Bayer AG
Geschäftsbereich Pflanzenschutz
Entwicklung / Registrierung
Pflanzenschutzzentrum Monheim
D-51368 Leverkusen

Person to contact:

[redacted]

b) K&N Efthymiadis SA
57022 Sindos
Industrial area of Thessaloniki
Greece, PO Box 48

[redacted]

1.2.2 Manufacturer of the active substance (IIA 1.2)

Manufacturer and contact point:

[redacted]

Person to contact: as applicant

Location of plant: as manufacturer

[redacted]

Person to contact:

[redacted]

Location of plant:

[redacted]

1.2.3 ISO common name and synonyms (IIA 1.3)

ISO: Methamidophos, no synonyms

1.2.4 Chemical name (IIA 1.4)

IUPAC: Thiophosphoramidic acid, O,S-dimethyl ester

CA: Phosphoramidothioic acid, O,S-dimethyl ester

1.2.5 Manufacturer's development code number(s) (IIA 1.5)

(a) SRA 5172

(b) AIT 003 (SHINUNG)

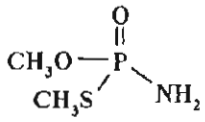
1.2.6 CAS, EU, EINECS, and CIPAC numbers (IIA 1.6)

CAS number:	10265-92-6
EEC number:	015-095-00-4
EINECS number:	233-606-0
CIPAC number:	355

1.2.7 Molecular formula, molecular mass and structural formula (IIA 1.7)

Molecular formula: $C_2H_8NO_2PS$

Structural formula:

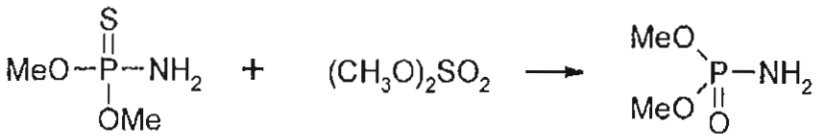


Molecular mass: 141.1 g/mol

1.2.8 Method of manufacture (IIA 1.8)

(a) Confidential information – see Annex C

(b) The only information provided is:



1.2.9 Specification of purity of the active substance (IIA 1.9)

Confidential information – see Annex C

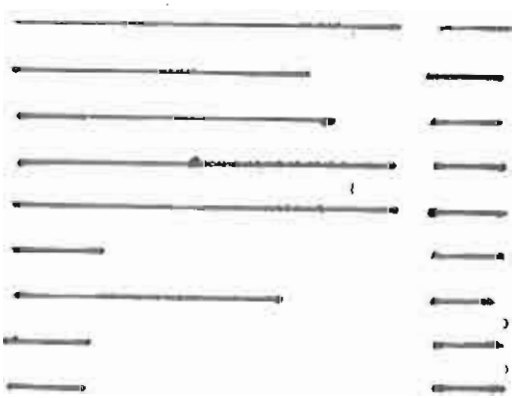
1.2.10 Identity of inactive isomers, impurities and additives (Annex IIA 1.10)

Impurities

(a) Confidential information – see Annex C

Impurities

(b)



1.2.11 Analytical profile of batches (IIA 1.11)

Confidential information - see Annex C

1.3 Identity of the plant protection product (IIA 3.1; IIIA 1)

1.3.1 (a) Current, former and proposed trade names and development code numbers (IIIA 1.3)

Plant protection product submitted for evaluation:

Trade name: Tamaron SL 200 blau

Manufacturer's product number: 0174737 (provisional prod. no.)

Trade name: Tamaron SL 600

Manufacturer's product number: 926523

1.3.1 (b) Current, former and proposed trade names and development code numbers (IIIA 1.3)

Plant protection product submitted for evaluation:

Trade name: Methaphos 60 SL

Manufacturer's product number:

1.3.2 (a) Manufacturer of the plant protection product (IIIA 1.1, 1.2)

Applicant:

Bayer AG Geschäftsbereich Pflanzenschutz

Entwicklung / Registrierung

Pflanzenschutzzentrum Monheim

D-51368 Leverkusen

Germany

[redacted]

Manufacturer:

[redacted]

1.3.2 (b) Manufacturer of the plant protection product (IIIA 1.1, 1.2)

[redacted]

Taiwan, ROC

1.3.3 (a) Type of the preparation and code (IIIA 1.5)

Soluble concentrate (SL)

1.3.3 (b) Type of the preparation and code (IIIA 1.5)

Soluble concentrate (SL)

1.3.4 (a) Function (IIIA 1.6)

Insecticide

1.3.4 (b) Function (IIIA 1.6)

Insecticide and acaricide

1.3.5 (a) Composition of the preparation (IIIA 1.4)

Confidential information – see Annex C

1.3.5 (b) Composition of the preparation (IIIA 1.4)

Content of technical active substance:	833 g/l
Content of pure active substance:	608.09 g/l
Further information:	Confidential information – see Annex C

1.4 Uses of the plant protection product

1.4.1 Field of use (IIA 3.3; IIIA 3.1)

Agriculture, horticulture (field and protected crops), viticulture

1.4.2 Effects on harmful organism (II A.3.2)

Contact and stomach poison

1.4.3 (a) Summary of intended uses (IIA 3.4; IIIA 3.3 to 3.7, 3.9)

1.4.3a-1 Harmful organism controlled and rates of application

Crop	harmful organisms controlled	Water volume l / ha	application rate kg a.i. / ha	* Maximum concentration (kg a.i. / 100 l)	Application no. / timing**
apple	aphidina, lepidoptera, psyllidae, tetranychidae	830-2000	0.5 - 1.2	0.06	1 - 2
beet, fodder	aphidina, diptera	280-400	0.35 - 0.5	0.125	1 - 2
beet, sugar	aphidina, diptera	280-400	0.35 - 0.5	0.125	1 - 2
cabbage (red, white, savoy)	aphidina, homoptera	600	0.36	0.06	1 - 2
cucumber	aleurodidae, aphidina, lepidoptera, thysanoptera	500-2000	0.3 - 1.2	0.06	1 - 3

* Concentration of active substance in diluted spray

** at infestation

Crop	harmful organisms controlled	Water volume l / ha	application rate kg a.i. / ha	* Maximum concentration (kg a.i. / 100 l)	Application no. / timing**
flowering brassica (couliflower and broccoli)	aphidina, homoptera	600	0.36	0.06	1 - 2
kohlrabi	aphidina, homoptera	600	0.36	0.06	1 - 2
maize / corn	aleurodidae, aphidina, lepidoptera	480-800	0.48 - 0.8	0.1	1 - 2
ornamentals (incl. closed forest)	aleurodidae, aphidina, lepidoptera, tetranychidae, thysanoptera	670-2000	0.4 - 1.2	0.06	2 - 3
peach	aleurodidae, aphidina, lepidoptera	1000-1500	0.5 - 0.75	0.05	1 - 2
pear	aphidina, lepidoptera, psyllidae, thysanoptera	830-2000	0.5 - 1.2	0.06	1 - 2
pepper, sweet	aphidina, lepidoptera, thysanoptera	500-2000	0.3 - 1.2	0.06	1 - 3
potato (Northern Europe)	aphidina, coleoptera	270-400	0.49 - 0.72	0.18	1 - 7
potato (Southern Europe)	aleurodidae, aphidina, lepidoptera, thysanoptera	530-700	0.315 - 0.63	0.09	1 - 3
tobacco	aphidina, cicadina, thysanoptera	600-1000	0.45 - 0.75	0.075	1 - 3
tomato	aleurodidae, aphidina, lepidoptera, thysanoptera	800 - 2000	0.48 - 1.2	0.06	1 - 3

* Concentration of active substance in diluted spray

** at infestation

1.4.3a-2 Summary of intended uses

Crop	Region	Use	Application rate				PHI
			l/ha	kg a.s./ha	no./timing**	(kg a.i./hl)	
Pome fruit [1]	S	F	830-2000	0.5-1.2	1-2	0.06	21
Peach[1] [2] incl. nectarine	S	F	1000-1500	0.5-0.75	1-2	0.05	21
Tomato	S	G/F	800-2000	0.48-1.2	1-3	0.06	7
Pepper, sweet[1]	S	G/F	500-2000	0.3-1.2	1-3	0.06	7
Cucumber	S	G/F	500-2000	0.3-1.2	1-3	0.06	7
Fowering brassica[1] (Cauliflower/Broccoli)	N	F	600	0.36	1-2	0.06	21
Cabbage (red, white, Savoy)	N	F	600	0.36	1 -2	0.06	21
Kohlrabi	N	F	600	0.36	1- 2	0.06	14
Potatoes [3]	N	F	270-400	0.49-0.72	1-7	0.18	21
Potatoes	S	F	350-700	0.315-0.63	1-3	0.09	21
Maize / Corn	S	F	480-800	0.48-0.8	1-2	0.1	60
Sugar an fodder beet	N+S	F	280-400	0.35-0.5	1-2	0.125	28 beet, 90 leaf for silage [4]
Tobacco [2]	S	F	600-1000	0.45-0.75	1-3	0.075	7/21
Ornamentals (incl. losed forest)	N+S	G/F	670-2000	0.4-1.2	2-3	0.06	n.a.

S = Southern Europe N = Northern Europe G = greenhouse F = field n.a. = not applicable

* Concentration of active substance in diluted spray

** at infestation

1) Crop with an 'open position' MRL in Directive 93/58/EEC

2) For peaches and tobacco the proposed critical use patterns of the combination product Tamaron & Confidor has been included. This product is under development and not registered in EU Member States. PHIs of 21 days (peach) and 7 days (tobacco) are proposed. The registered uses of Tamaron require for peaches and tobacco a PHI of 21 days

3) The critical use pattern for potatoes in Germany covers the control of viruses transmitting aphids in seed potatoes (1-7 x 0.48 - 0.6 kg ai/ha), Colorado beetle (1x) at infestation.

4) Sugar beet leaves are not fed to cattle before 90 days after the last treatment because of the time needed for silage production. Residue studies show that residues are below the LOQ of 0.01 mg/kg after that period

1.4.3 (b) Summary of intended uses (IIA 3.4; IIIA 3.3 to 3.7, 3.9)

1.4.3a-2 Summary of intended uses

Not supported by data (supervised trials).

Crop	Country Region	Use (G/F)	Rate and No. of application (kg a.i./ha)	No.	Time of application	Pre-harvest interval (days)
Peach-appricots	S	F	1.12-1.5	2	Before harvesting	21
Apple-pears	S	F	1.12-1.5	2	Before harvesting	21
Almonds	S	F	0.9 - 1.2	2	Till end of May	21
Tomato	S	F	0.9 - 1.35	2	Before harvesting	21
Grapes	S	F	0.7-0.9	2	Before harvesting	21
Corn	S	F	0.75-1.1	2	Till formation of seeds	21
Cotton	S	F	0.6-1.5	2	Before harvesting	21
Onion	S	F	0.3-0.45	2	Before harvesting	21
Aubergine	S	F	0.6-0.9	2	Before harvesting	21
Cauliflower	S	F	0.6-0.9	2	Before harvesting	21
Cabbage	S	F	0.6-0.9	2	Before harvesting	21
Lettuce	S	F	0.48-0.72	2	Before harvesting	21
Potato	S	F	0.45-0.9	2	Before harvesting	21
Tobacco	S	F	0.45 - 0.9	3	Before harvesting	21
Ornamentals	S	F	0.6	2	Before harvesting	n.a.

S = Southern Europe N = Northern Europe G = greenhouse F = field n.a. = not applicable

1.4.4 (a) Information on authorisations and registrations in the EU Member States (IIIA 12.1)

Table 1.4.4a-1: Authorizations and Registrations in the EU

Country	**Company Type of authorisation**	**Crops**	**Authorisation details**
Austria	Bayer AG commercial	ornamentals	Tamaron 600 g/ltr. EC Reg. No.: 2163 Iss. date: 04/84 Exp. date: 12/01
Belgium	Bayer AG commercial	forest, ornamentals	Tamaron 200 g/ltr. SL Reg. No.: 6901/B Iss. date: 03/72 Exp. date:
France	Bayer AG commercial	apple, apricot, grape, peach, pear, plum	Tamaron 400 g/ltr. EC Reg. No.: 7200153 Iss. date: 01/72 Exp. date:
France	Tomen commercial	apple, grape, peach	Orthotox 400 g/ltr. Reg. No.: 7700187 Iss. date: Exp. date:

Country	Company Type of authorisation	Crops	Authorisation details
Germany	Bayer AG commercial	beet, cabbage, cauliflower, hop, kohlrabi, ornamentals, potato	Tamaron 600 g/ltr. SL Reg. No.: 32189 Iss. date: 01/72 Exp. date:
Greece	Bayer AG commercial	almond, apple, aubergine, cauliflower, cotton, cucumber, grape, lettuce, maize, onion, ornamen-tals, pear, pepper, potato, tobacco, tomato, vegetables	Tamaron 600 g/ltr. SL Reg. No.: 1246 Iss. date: 02/80 Exp. date:
Greece	Tomen commercial	cotton, hop, maize, ornamentals, potato, tobacco, vegetables	Monitor 60 SL 600 g/ltr. SL Reg. No.: 1201 Iss. date: 03/83 Exp. date:
Italy	Bayer AG commercial	apple, beet, grape, maize, ornamentals, pear, potato, prunus, soybean, strawberry	Tamaron 200 g/ltr. SL Reg. No.: 0813 Iss. date: 03/84 Exp. date:
Italy	Bayer AG commercial	apple, beet, grape, maize, ornamentals, peach, pear, strawberry	Bayteroid TM 500 g/ltr. EC (+ 25 g/l cyfluthrin) Reg. No.: 8041 Iss. date: 03/92 Exp. date:
Netherlands	Bayer AG commercial	potato	Tamaron 200 g/ltr. EC Reg. No.: 7362 N Iss. date: 07/78 Exp. date:12/96
Portugal	Bayer AG commercial	peach, potato, tomato	Tamaron 600 g/ltr. SL Reg. No.: 1311 Iss. date: 02/75 Exp. date:
Spain	Bayer AG commercial	citrus, cotton, maize, ornamentals, pome fruit, stone fruit	Tamaron 50 LS 500 g/ltr. SL Reg. No.: 11693 Iss. date: 05/77 Exp. date: 09/96
Spain	Tomen commercial	citrus, cotton, cucumber, maize, ornamentals, pepper, stone fruit, tomato	Monitor 60 600 g/ltr. EC Reg. No.: 13700 Iss. date: Exp. date:

1.4.4 (b) Information on authorisations and registrations in the EU Member States (IIIA 12.1)

Table 1.4.4a-1: Authorizations and Registrations in the EU

Product	Country	Commercial Name	Type of Authorisation	Crop/Uses	Registration Date	Re-registration	Registration No.
60 SL (Methamidophos 60% w/v)	Greece	Comet/Methaphos 60 SL	Commercial	Insecticide, acaricide	17.04.84	December 1993	1477

LEVEL 2

Reasoned statement of the overall conclusions drawn by the Rapporteaur Member State

Methamidophos

2.1.1 Identity

All points of IIA and IIIA Section 1 have been addressed and the information supplied is generally acceptable. Analytical profile of batches were submitted (point 1.3.11, IIA 1.11).

2.1.2 Physical, chemical properties

Methamidophos is an organophosphate insecticide which is not resolved into its optical isomeres. Its vapor pressure is low and its water solubility is high. It is rapidly and extensively degraded by aqueous hydrolysis and photolysis. Its log P_{ow} is low (-0.80) and therefore it has little potential to bioaccumulate. Its flammability, flash point, and explosive and oxidizing properties indicate that it poses no hazard.

Tamaron SL 200 and Tamaron SL 600 are both not explosive, not oxidising, and their pH is within the range that naturally occurs e.g. in soil. Stability allows storage under practical and commercial conditions. The technical properties indicate that no particular problems have to be expexted, when either one of these two formulations is used as recommended.

The information provided by notifier (b) was in general not acceptable.

2.1.3 Details of uses and further information

The information supplied on uses adequately addresses the requirements of ANNEX II A Sections 3.1 to 3.5 and Annex III a Section 3.

Information supplied addresses methods for handling the active substance and plant protection product.

The information provided by notifier (b) was in general not acceptable.

2.1.4 Classification and labelling

2.1.4.1 Methamidophos

Hazard symbol:		T+, N
Indication of danger:		very toxic
Risk phrases:	R 24:	Toxic in contact with skin.
	R 28:	Very toxic if swallowed.
	R 36:	Irritating to eyes.
	R 50:	Very toxic to aquatic organism
	R 53:	May cause long-term adverse effects in the aquatic environment.
Safety phrases:	S 28:	After contact with skin, wash immediately with plenty of water and soap.
	S 36/37:	Wear suitable protective clothing / Wear suitable gloves.
	S 45:	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

Justification for the proposal

Very Toxic

The acute oral toxicity (LD_{50}) in rats was found to be <25 mg/kg bw.

R 24 The classification toxic to skin results from the acute dermal toxicity.

	The dermal LD_{50} was found to be between 50 mg/kg bw and 400 mg/kg bw.
R 28	The classification "very toxic" results from the acute oral toxicity.
R 36	Follows from the scores of the eye irritation test.
R 50, R 53:	High toxicity to aquatic organism
S 28	Obligatory for all very toxic substances; in case of skin contamination water and soap are indicated to reduce the exposure.
S 36/37	Obligatory for all very toxic substances.
S 45	Obligatory for all very toxic and corrosive substances.

2.1.4.2 **Tamaron SL 200**

Proposals for the classification and labelling

Hazard symbol(s): T, N

Indications of danger: Toxic

Proposals for risk and safety phrases in accordance with Article 15(1), (g) and (h)

Risk phrases:	R 21	Harmful in contact with skin.
	R 25	Toxic if swallowed.
	R 50:	Very toxic to aquatic organism
	R 53:	May cause long-term adverse effects in the aquatic environment.
Safety phrases:	S 28	After contact with skin, wash immediately with plenty of water and soap.
	S 36/37	Wear suitable protective clothing and suitable gloves.
	S 45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

Justifications for the proposal

Toxic:	The acute oral toxicity value (LD_{50}) was found to be > 25 and < 200 mg/kg b.w.
R 25:	Follows from the acute oral toxicity value.
R 21:	Follows from the acute dermal toxicity value ($200 < LD_{50} < 2000$ mg/kg b.w.).
R 50, R 53:	High toxicity to aquatic organism
S 28:	Recommended for toxic substances and formulations; water and soap are indicated to reduce skin contamination.
S 36/37:	Obligatory for all toxic substances labeled with R 21.
S 45	Recommended for toxic substances and formulations.

2.4.1.3 **Tamaron SL 600**

Proposals for the classification and labelling

Hazard symbol(s): T+, N

Indications of danger: Very toxic

Proposals for risk and safety phrases in accordance with Article 15(1), (g) and (h)

Risk phrases:	R 24	Toxic in contact with skin.
	R 28	Very toxic if swallowed.
	R 50:	Very toxic to aquatic organism
	R 53:	May cause long-term adverse effects in the aquatic environment.
Safety phrases:	S 28	After contact with skin, wash immediately with plenty of water and soap.
	S 36/37	Wear suitable protective clothing and suitable gloves.
	S 45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

Justifications for the proposal

Very toxic:	The acute oral toxicity value (LD_{50}) was found to be < 25 mg/kg b.w.
R 28:	Follows from the acute oral toxicity value.
R 24:	Follows from the acute dermal toxicity value of male rats (192 mg/kg b.w.).

The range for classification as "toxic" by the dermal route is $50 < LD_{50} \leq 400$ mg/kg b.w. The test results for female rats (49 mg/kg b.w.) slightly exceed this range. However, this result must be regarded as approximative and is not representative for the dermal toxicity of Tamaron SL 600. Therefore R 24 is justified.

R 50, R 53:	High toxicity to aquatic organism
S 28:	Obligatory for all very toxic substances and formulations; in case of skin contamination water and soap are indicated to reduce the exposure.
S 36/37:	Obligatory for all very toxic substances and formulations.
S 45:	Obligatory for all very toxic and corrosive substances and formulations.

2.2 Methods of analysis

For the determination of pure active substance and impurities in the technical active substance and in formulated products, methods based on HPLC, TLC and capillary gas chromatography are available.

Several methods of analysis have been submitted by the main notifier Bayer/Tomen for evaluating residues of methamidophos in plant materials, processed products, animal tissues as well as in environmental samples such as soil, water, and air.

Methamidophos is extracted from the different matrices using various solvents including ethyl acetate, acetone and methanol. Either methamidophos is salted out by adding sodium chloride, or the water is bound by adding anhydrous sodium sulfate. Extracts are further cleaned up using liquid-liquid partitioning and/or silica gel column chromatography and/or gel permeation chromatography. The extraction step chosen depends on the water and/or oil content of the sample material. Air is pumped through Tenax or XAD-2 adsorption tubes. The adsorbed methamidophos is extracted with n-butyl acetate.

Methamidophos is determined by gas chromatography on packed polar columns. Newer methods use wide-bore columns. Various detectors have been used, including thermionic and flame ionization with the flame photometric detector being more selective than thermionic detectors.

These methods, because of their high degree of specifity, can also be used for enforcement purposes.

A summary of the enforcement methods validation is given in the table below.

Substrate	Spiking Level	Range of Recoveries	Limit of determination
plants	0.011 - 0.168 mg/kg	78 - 96 %	0.01 mg/kg
soil	0.01 - 1.0 mg/kg	75 - 114 %	0.01 mg/kg
water	0.05 - 100 µg/l	80 - 100 %	0.05 - 0.1 µg/l
air	0.0008 - 0.029 mg/m³	78 - 107 %	0.0008 mg a.i./m³
animal and human body fluids and tissues	0.01 - 0.1 mg/kg	45 - 120 %	0.01 - 0.02 mg/kg for tissues 0.004 mg/kg for milk

Conclusion

Due to the formula of methamidophos and its chemical and physical properties, the analytical difficulties and advantages arising in the analysis of residues are well known regarding the qualitative or the quantitative approaches (qualitative advantage: phosporous selective detection; quantitative difficulty: extraction out of water rich phases).

On the basis of this consideration it can be judged that adequate methodology exists for the determination of residues of methamidophos in all relevant matrices (plant, processed products, soil, water, air, and animal tissues).

2.3 Impact on human and animal health

2.3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to their transformation products

Absorption, distribution, excretion and metabolism

The metabolism studies in rats show a rapid absorption of the radioactivity followed by fast distribution in organs and tissues and a rapid elimination from the body after oral and intravenous administrations. 50 - 77% of the administered dose is eliminated within the first 1 to 3 days after dosing.

The major part of the applied radioactivity is eliminated via urine, expired CO_2 and feces. A part of the radioactivity is incorporated into body constituents in form of $^{14}C_1$-fragments and eliminated in accordance with the natural turnover of these compounds.

Metabolism studies in rats show that methamidophos is rapidly degraded through deamination and/or demethylation. The first step is cleavage of either P-O, P-N, or P-S bonds followed by demethylation. In

addition to unchanged methamidophos the following major metabolites are found:desamino-methamidophos, *mono methyl phosphate*, S-methyl *thiophosphoric acid*, *methyl phosphoramidate*, S-methyl phosphoramidothioate, phosphoric acid and carbon dioxide. In plant metabolism studies, methanesulfonic acid is identified as a degradation product of methamidphos. This metabolite is not detected in the rat. In plants, methanesulfonic acid has to be regarded as an oxidation product of methyl mercaptan. It is highly likely that methyl mercaptan is also a degradation product of methamidophos in the animal. Studies concerning the metabolic behaviour of methyl mercaptan in-vivo (rats) and in-vitro (whole blood) show that this compound is rapidly oxidised to carbon dioxide and sulfate. Methanesulfonic acid is detected as an oxidation product of methyl mercaptan incubated with whole blood.

Methamidophos administered orally to lactating goats is quickly absorbed and distributed with the blood in all organs and tissues. Methamidophos is rapidly metabolised and about half of the administered radioactivity is excreted quickly. This excreted radioactivity is distributed mainly between the breath and the urine and, to a lesser extent, the feces and milk. The remaining radioactivity which is relatively uniformly distributed in the organs and tissues, is eliminated at a slower but constant rate.
Characterisation of the residues in the tissues and milk show that most of the radiolabelled residues are natural products, like glucose and galactose, phosphatidylcholine and other phospholipids, choline and amino acids, indicating that the S-methyl-^{14}C is released and incorporated into the metabolic pool.
Methamidophos is desaminated in the goat to desamino-methamidophos found in liver, kidney and urine. By cleavage of the P-O bond S-methyl phosphoramidothioate is formed, which is present in the kidney.

Metabolism studies in hens indicate that methamidophos is rapidly absorbed and dispersed throughout the entire bird. Methamidophos is very quickly and thoroughly metabolised in the organs and tissues of laying hens. Methamidophos is metabolised in the laying hen to desamino-methamidophos, found in liver, muscle, fat and egg and S-methyl phosphoramidothioate which is detected in liver, fat and egg white.
It appears that metabolised methamidophos enteres the carbon-1 pool and is incorporated into natural plant products.
Characterisation of the residues in tissues show that the major part of the radiolabelled residues in the extracts and post extraction solids is represented by natural products including methionine, choline, phosphatidylcholine and other phospholipids. Phosphatidylcholine, other less polar phospholipids and lipids and proteins are the major radiolabelled components in the eggs.

Dermal absorption

An in vitro study show that relative percutaneous absorption of technical grade methamidophos through human skin, during 24-hours continuous exposure, was less than 1% of the applied dose, both for concentrate formulation and aqueous dilution. Rat skin membranes were about 121 times more permeable than human skin for the concentrate formulation and 13 times more permeable for the aqueous dilution.

In vivo percutaneous absorption of analytical grade methamidophos through rat skin is time-dependent and, at 24 hours, was 40-44% for dermal doses of 0.05-5 mg.

From these studies the Notifier A derives a dermal absorption rate of 3.38%.

The RMS considers a more conservative value of 5% should be used.

Mammalian toxicity

Methamidophos is a cholinesterase inhibitor characterised by high acute toxicity.

Acute toxicity

Acute toxicity is accompanied by typical cholinergic signs that appear within a few hours after exposure to methamidophos. Death in humans upon poisoning and in experimental animals upon exposure occurs within a few hours up to five days. A complete recovery occurs within seven days of dosing.

Dermal irritation

Methamidophos is a mild dermal irritant and is slightly irritating to rabbit eyes.

Skin sensitisation

It is not a skin sensitiser.

Tamaron SL 200 has high acute oral and moderate acute dermal toxicity. It is not irritant to the skin and slightly irritant to the eye.

Tamaron SL 600 has very high acute oral and high acute dermal toxicity. It is not irritant to the skin and eye.

Summary of acute toxicity

Toxicological study	*Methamidophos*	*Tamaron SL 200*	*Tamaron SL 600*
LD_{50}, oral, rat	13.0 - 31.9* mg/kg b.w.	55 - 56* mg/kg b.w.	18 - 20* mg/kg b.w.
LD_{50}, oral, mouse	10.5 - 29.6* mg/kg b.w.		
LD_{50}, oral, guinea pig	30 - 50 mg/kg b.w.		
LD_{50}, oral, rabbit	10 - 30 mg/kg b.w.		
LD_{50}, oral, cat	10 - 30 mg/kg b.w.		
LD_{50}, oral, dog	10 - 30 mg/kg b.w.		
LD_{50}, oral, hen	25 - 82 mg/kg b.w.		
LD_{50}, dermal, rat / 24 h	108 - 162 mg/kg b.w.	553 - 778* mg/kg b.w.	49 - 192* mg/kg b.w.
LD_{50}, dermal, rat / 4 h	110 - 380.2 mg/kg b.w.		
LD_{50}, dermal, rat / 7 days	50 mg/kg b.w.		
LD_{50}, dermal, rabbit / 24 h	69.1 - 122.2 mg/kg b.w.		
LD_{50}, dermal, hen	50 mg/kg b.w.		
LC_{50}, inhalation, rat / 1 h	241 - 377 mg/m³ air		
LC_{50}, inhalation, rat / 4 h	63.2 - 213 mg/m³ air	252 mg/m³ air	252 mg/m³ air
LC_{50}, inhalation, rat / 5 days (6 h/day)	> 33.1 mg/m³ air		
LD_{50}, intraperitoneal, rat	15 - 26.4 mg/kg b.w.		
LD_{50}, intraperitoneal, mouse	5.3 - 11.55 mg/kg b.w.		
LD_{50}, intraperitoneal, hen	~10 mg/kg b.w.		
skin irritation, rabbit	mild irritant	not irritant	not irritant
eye irritation, rabbit	slight irritant	slightly irritant	not irritant
skin sensitisation, guinea pig	not sensitising	no indication for skin sensitisation	no indication for skin sensitisation

*The range of results given covers variations due to vehicle, sex, and dosing conditions.

Short-term toxicity

Effects of methamidophos on repeated exposure are limited mainly to those associated with cholinesterase (ChE) inhibition. Because of its rapid metabolism and excretion of its metabolites, methamidophos does not accumulate in the body. Its cumulative toxicity following 60 consecutive days of administration in rats is similar to that seen after a single dose. A complete and rapid reversal of ChE inhibition is seen after exposure is terminated.

Long term toxicity

Long-term exposure of rats, dogs and mice to methamidophos caused significant ChE inhibition, which was the most sensitive toxicity endpoint. During a recovery period of two to four weeks, after subchronic exposure, ChE reverted to normal levels in rats. No evidence of any organ damage was observed at the highest doses tested in these studies.

Mutagenicity

The genotoxic potential of Methamidophos was studied in a number of in vitro test systems in bacteria and in mammalian cells as well as in several in vivo tests in mammals, covering the following endpoints: point mutations, chromosome aberrations, and DNA damage.

The results obtained did not show any evidence of Methamidophos genotoxicity. Weak positive results were obtained in some cytogenetic *in vivo* and *in vitro* assays. These results were not confirmed in further experiments properly carried out.

In conclusion there is no concern for mutagenicity of Methamidophos.

Oncogenicity

There was no evidence for oncogenic potential of methamidophos in rats or mice.

Reproductive toxicity

The exposure of male and female rats to methamidophos through the diet for two generations was unable to produce adverse effects on fertility and reproductive parameters. The high doses reduced the adult body weight gain, the pup weights and weight gains during lactation.

There were no embryotoxic or teratogenic effects in rabbits following exposure during gestation at maternally toxic doses. In rats there were no teratogenic effects. A reduced fetal weight was observed in relation to maternal toxicity characterised by body weight depression.

Neurotoxicity

Numerous acute oral delayed neurotoxicity tests in hens protected with atropine/pralidoxime therapy have shown that racemic methamidophos will not cause obvious clinical signs of delayed neuropathy in hens in single doses of less than about 200 mg/kg b.w. (about 8 x the unprotected LD_{50}). Histopathologic confirmation of the absence of neuropathy was demonstrated at 50 mg/kg b.w. A 400 mg/kg b.w. single dose of racemic methamidophos resulted in weak to moderate clinical signs of delayed neuropathy (no histopathologic evaluation was done) in three of the birds surviving this dose. A study with the enantiomers

of methamidophos evaluating clinical signs of OPIDP suggests that the (+)methamidophos is responsible for the delayed neurotoxic potential of the racemate; however, this enantiomer demonstrates OPIDP at supra-lethal doses only.

Inhibition of Neurotoxic Esterase in the 70 to 80% range and aging of NTE are generally considered necessary to induce OPIDP after single applications. A comparative acute oral study of NTE inhibition and aging with the enantiomers of methamidophos in hens showed that (+)methamidophos leads to greater inhibition, but nearly complete recovery; while (-)methamidophos shows less potent inhibition, but activity is less restorable. NTE inhibition in the OPIDP threshold range and aging of NTE were demonstrated for (-) methamidophos at a single dose of 400 mg/kg b.w. (5 x LD_{50}). These results correlate well with the oral study with (+)methamidophos, which demonstrated weak neuropathic potential only at 400 mg/kg b.w. In all cases it is evident that there is a very high threshold dose (multiples of the unprotected lethal dose) for delayed neuropathy resulting from acute oral doses of methamidophos in hens.

The results of the delayed neurotoxicity tests in hens indicate that no risk of delayed neuropathy is anticipated to workers under normal exposure conditions. The above data indicate that extremely high oral doses in humans, subsequently treated with vigorous antidote therapy and respiratory support, might result in delayed neuropathy in some of the survivors. This prediction is confirmed by the observations of acute poisoning cases later summarised in this document.

Several studies show that Methamidophos is a weak inhibitor of cholinesterases in vitro, based on the rate constant for the ChE inhibition (k_i 1.1± 0.2x10^3 M^{-1}.min^{-1}).

Interactions of methamidophos with neuropathy target esterase (NTE) have indicated that methamidophos is also a relatively poor inhibitor of NTE. In vitro experiments indicated that Methamidophos is a weaker inhibitor of NTE than of AchE.

For in vivo situations, methamidophos has been shown either to protect against development of delayed neurotoxicity by another neurotoxic agent (di-n-butyl 2,2-dichlorovinylphosphate [DBDCVP]) or to promote the neurotoxicity of that agent, depending on the dose and dosing scheme. When given before DBDCVP in high doses (50 mg/kg), methamidophos protects against neuropathy; but if given after DBDCVP, methamidophos promotes neurotoxicity.

Acute and subchronic oral neurotoxicity screening tests in rats, including functional observation battery and motor activity assessments, have shown only the anticipated neurotoxic symptoms associated with ChE inhibition. No delayed neurotoxic effects were seen, and symptoms were reversible in surviving rats. There was no histopathologic evidence of an adverse effect on the nervous system in these studies.

In conclusion, the relatively higher potency of methamidophos for inhibition of AChE compared with NTE of both man and hens makes the development of delayed neuropathy possible only after severe (potentially

fatal) acute intoxications. Rat screening studies have shown no potential for delayed neurotoxicity, or for neurotoxic effects other than the anticipated signs related to cholinesterase inhibition. The hen, however, which is a species more sensitive to OPIDP, has demonstrated this effect only at extremely high doses (the effective dose for the racemic compound is 12-16 x unprotected LD_{50}). There appears to be acceptable clinical evidence that massive overdoses of methamidophos can cause delayed neuropathy in some human cases. No risk for delayed neuropathy in man exists in the absence of marked acute cholinergic toxicity.

Results of short-term toxicity, long-term toxicity, mutagenicity, teratogenicity and neurotoxicity testing

Type of study	*Test species*	*Result obtained with the most sensitive test species*
oral, 56 days	rat	NOEL: 0.5 ppm (0.03 mg/kg b.w./day)
oral, 90 days	rat, dog	NOEL: 2 ppm (0.13 - 0.17 mg/kg b.w./day), rat; 1.5 ppm (0.039 mg/kg b.w./day), dog
dermal, 15 x 6 h/day	rabbit	NOEL: 0.5 mg/kg b.w./day
inhalation, 15 x 6 h	rat	NOEL: 2.6 mg/m^3 air
inhalation, 63 x 6 h	rat	NOEL: 1.1 mg/m^3 air (0.3 mg/kg bw/day)
mutagenicity	bacteria; mammalian cells in vitro; in vivo	negative: in all assays (4 out of 4); negative except for 3 positive in vitro tests out of 9; 4 positive in vivo assays out of 12
acute neurotoxicity	rat	NOEL: < 1 mg/kg b.w.
90-day neurotoxicity	rat	NOEL: 1 ppm (0.05 mg/kg b.w./day)
oral, 2 years	rat	NOEL: 2 ppm (0.1 mg/kg b.w./day)
oral, 12 months	dog	NOEL: 2 ppm (0.06 mg/kg b.w./day)
oral, 2 years	mouse	NOEL: 5 ppm (0.67/0.78 m/w mg/kg b.w./day)
oncogenicity	rat, mouse	negative
2 generation	rat	NOEL: 10 ppm (0.5 mg/kg b.w./day)
fertility	mouse	NOEL: 0.2 mg/kg b.w./day; supplementary study
teratogenicity	rat, rabbit	no primary teratogenic/embryotoxic potential
delayed neurotoxicity acute, oral	hen	NOEL: >50 mg/kg b.w. for delayed neuropathy
delayed neurotoxicity acute, dermal	hen	NOEL: 200 mg/kg b.w.
delayed neurotoxicity 90-day, oral	hen	NOEL: 0.3 mg/kg b.w./day for neuropathy target esterase (NTE) inhibition (no delayed neurotoxicity up to 3.0 mg/kg b.w./day)
delayed neurotoxicity 90-day, dermal	hen	NOEL: 1.5 mg/kg b.w./day for NTE inhibition (no delayed neurotoxicity up to 4.5 mg/kg b.w./day)

Antidotal studies

Studies of antidotal treatment of methamidophos intoxication have indicated that the LD_{50} for rats treated with atropine or pralidoxime increased approximately four-fold compared with the unprotected LD_{50} value in rats, indicating that these agents can protect against acute methamidophos poisoning. Some publications

report about cases of acute poisonoing with suicidal intentions in man. Patients were treated with atropine, pralidoxime and respiratory support with complete recovery of health conditions.

Immunotoxicity

The effects of methamidophos on the immune system have been investigated and no primary immunotoxic effects were observed in studies with mice and rats. Nevertheless secondary immune system reactions were noted, probably stress-induced; results are consistent with the effects of other organophosphorus pesticides (OPs) on immune system function. These results indicate that glucocorticoids probably mediate the effect of OPs on the immune system at high doses.

Data on humans

Several reports on cases of neuropathy attributed to Methamidophos are present in the literature. Some Authors claim that this compound would induce a peripheral neuropathy starting a few days after severe overexposure (so called '*intermediate syndrome*'). The clinical, pathological and functional features of these neuropathies have been extensively discussed in the literature, leading to conclude that the existence of this disease as a separate nosological entity is not yet demonstrated.

A combination toxicity study on human volunteers using methamidophos and acephate in 1:4 and 1:9 mixtures of methamidophos:acephate gives reliable information on the NOAEL in man. No effect on erythrocyte ChE activity was detected at any time during the study. The NOAEL was 0.2 mg/kg b.w./day for the 1:4 mixture, and 0.3 mg/kg b.w./day for the 1:9 mixture. Several metabolism studies reported that only 1-1.5% (as a maximum) of acephate is metabolised to methamidophos. Moreover IC_{50} of acephate and methamidophos differ greatly (methamidophos is a 70-100-fold more potent AchE inhibitor than acephate). Comparison of LD_{50} of the two compounds shows a 1:100 ratio. It is not possible to compare results of repeated dose studies because for acephate $NOEL_s$ are not available (studies established only $LOEL_s$) Considering 1:4 mixture, in which 20% is methamidophos and 80% is acephate, it can be concluded that the predominant part of cholinesterase inhibition is produced by methamidophos.

In light of these considerations it can be stated that the NOAEL of the human volunteer study is 0.04 mg/kg bw.

2.3.2 Acceptable daily intake (ADI)

Methamidophos was last evaluated in 1990 by the 'Joint Meeting on Pesticide Residues' (JMPR 1990). On the basis of available animal experimental data and the data obtained in a study on volunteers, an ADI of 0.004 mg/kg bw was established by the WHO Expert Commission.

Based on the data presented by the Notifiers, the results of :

- a 21 days oral study in man (NOAEL 0.04 mg/kg bw)
- a 56 days oral study in rat (NOEL 0.03 mg/kg bw)
- a 90 days neurotoxicity study in rat (NOEL 0.05 mg/kg bw)
- a 90 days oral study in dog (NOEL 0.03 mg/kg bw)

- a 12 months feeding study in dog (NOEL 0.06 mg/kg bw)

can be used for calculation of the acceptable daily intake.

As the ADI should be established on the basis of the NOAEL in the most relevant study and species, the human volunteer study can be considered as the most reliable. A safety factor of 10 should be applied, accounting for intraspecies variability. The proposed ADI for man is 0.004 mg/kg bw.

It can be noted that NOELs established in repeated dose-studies in rats and dogs were found to be in the same order of magnitude as the human study NOEL. This observation indicates the lack of interspecies differencies in sensitivity to the toxic effects of methamidophos. The RMS considers the human data preferable for the establishment of the ADI and draws the attention to the fact that the choice of NOAELs from animal studies would have led to comparable figures.

2.3.3 Acute Reference Dose

In light of the high acute toxicity of methamidophos it is necessary to allocate an acute reference dose.

The available studies relevant to the derivation of an ArfD are:

- 90-day neurotoxicity study in rat: NOEL 0.05 mg/kg bw (based on ChE inhibition)
- human-volunteer study with methamidophos:acephate 1:4 mixture: NOEL 0.04 mg/kg bw (based on ChE inhibition)

The study on humans can be considered the most reliable. Applying a 10-fold safety factor, accounting for the intraspecies variability, the proposed Acute Reference Dose is 0.004 mg/kg bw.

2.3.4 Acceptable operator exposure level (AOEL)

According to the principles of Annex VI to Directive 91/414 EEC, the proposed acceptable operator level should be established on the basis of the lowest dose at which no adverse effect is observed in the most relevant studies and species.

The calculation of an acceptable operator exposure level can be based on the results of the subacute toxicity study in volunteer human subjects. The NOEL = 0.04 mg/kg bw is used to calculate the AOEL. It is considered appropriate to apply a safety factor of 10, to account for intraspecies variability.

The proposed AOEL is 0.004 mg/kg bw.

Inhalation risk for workers (TLV)

Acute inhalatory NOEL is 1.1 mg/m^3, 6 hours/day, 5 times/week, for 3 months, corresponding to 0.3 mg/kg bw/day.

2.3.5 Drinking water limit

On the basis that exposure through drinking water should not account for more than 10 % of the ADI and assuming an average consumption of 2 litres of water per person per day and a body weight of 60 kg, a parametric value of 0.012 mg methamidophos per drinking water liter is proposed.

2.3.6 Impact on human or animal health arising from exposure to the active substance or to impurities contained in it

According to the Notifier A Tamaron 200 SL and 600 SL are intended to be used in fruits (pome fruit and peach), in vegetables (tomato, sweet pepper, cucumber, cauliflower, broccoli, cabbage and Kohlrabi), in potatoes, in corn, in sugar and fodder beets, in tobacco and in ornamentals. In the case of Tamaron 200 SL and 600 SL the operator exposure was estimated by the Notifier using the following model:

Uniform principles for safeguarding the health of applicators of Plant Protection Products (Uniform Principles for Operator Protection); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem; 277; 1993

Notifier A stated that:

- due to technical reasons (wind and hot temperature in southern Europe where OP are used predominantly) daily spraying can be restricted to 4 hours/day;
- in consequence reduced application areas have to be considered;
- this is a realistic approach based on the smaller farm size (0.5 –4 ha) in Southern

The end points on which the Notifier calculated the total systemic exposure were based on the following assumptions:

- treated areas in field crops tractor mounted scenarios: 10 ha
- treated areas in high crops tractor mounted scenarios: 4 ha
- treated areas in high crops hand held scenarios: 0.5 ha
- dermal absorption, based on an in vivo and an in vitro studies, was 3.38%
- the tolerable inhalative exposure is calculated considering 100% absorption of the inhaled methamidophos
- use rate: 1.2 kg a.i./ha
- an AOEL of 0.004 mg/kg bw.

The Notifier A produced an exposure estimate for six scenarios as follows:

- field crops, tractor mounted with no PPE
- field crops, tractor mounted with PPE
- high crops, tractor mounted with no PPE
- high crops, tractor mounted with PPE
- high crops, hand held with no PPE
- high crops, hand held with PPE.

When no PPE were used the calculated operator exposure was unsafe for the applicator. When PPE (namely gloves and standard protective garment), and tractors with closed cabs or hand held applications with closed systems were used, Tamaron 200SL and 600 SL were safe for the operator.

The RMS disagrees with some of the assumptions made by the Notifier in the calculation of exposure in the German model.

As the treated area size, the assumption of 4 hours/day work is not justified unless such a restriction is clearly part of the recommended method of use and, as such, included in the label. Thus the usual value of 8 hours and the corresponding areas of treatment should be used.

As to dermal absorption rate, the value used by the Notifier of 3.38%, derived from an in vitro study, is not completely reliable, therefore it is preferable to consider a conservative dermal absorption rate of 5%.

With these assumptions the calculated operator exposure, considering the use of the following PPE: gloves, filter mask, hat and standard protective garment, becomes unsafe only for the high crops tractor mounted scenario.

Since the % AOEL in the high crops tractor mounted scenario is at the higher level, the RMS proposes to consider the following options for further reducing the risk for the operators:

- to reduce the application rates at 1.0-1.1 kg a.i./day (in this case the saturation of AOEL would be 82-90% respectively)
- to reduce the daily time of application, including this limit in the GAP
- any combination of the above

Bystander exposure

The Notifier A has presented an estimation of the bystander exposure based on some definitions and assumptions, including the assumption that the bystander would leave the area of a potential exposure after a very short period of time (1 minute) due to inconvenience through contact with small droplets of spray drift, odor and noise of application machinery.

A calculation of exposure for the bystander with these assumptions shows no exeedence in comparison with AOEL = 0.004mg a.i./kg*d.

The RMS believes that these evaluations proposed by the Notifier A have limited relevance.

Bystanders may be exposed persons that accidentally walk through a treated crop or stand or live in the proximity of an area being treated: if 'Good Plant Protection Practices' are adopted during the application of pesticides, accidental exposure is not anticipated and must not take place, and therefore no AOEL is needed. If exposure takes place accidentally, the anticipated exposure pattern would be of an acute type and, in any case, difficult to quantify and to assess in term of risk. Adequate protective measures (marking the treated zone with light or acoustic signals, enclosing the crops) can and must be adopted to prevent accidental exposure.

Bystanders may also be 'residential bystanders', that is persons who permanently live close to crops being treated. These persons may be exposed through drift via inhalation and/or dermal absorption. The expected air concentrations as a function of the distance from the spray (high crops tractor mounted as a worst case) are as follows:

- 14.1% at 7.5 mt;
- 10.6% at 10 mt.
- 6.2% at 15 mt.
- 4.2% at 20 mt.
- 2.0% at 30 mt.

Therefore, on the basis of calculations accounting for:

- spray drift deposition in fruit crops;
- dermal penetration factor of 5%;
- exposure time: 1/60 of the exposure time of the applicator

the need of a buffer zone of 20 mt is recommended (corresponding to a spray drift deposition of 4.2%).

Worker exposure

The Notifier A has produced an estimation based on several assumptions including that workers re-enter the treated culture only after the spray has dried.

A general estimation of worker exposure directly after application in field crops and low crops calculated according to the formula:

D=FDR x TF x WR x AR x P

A general estimation of worker systemic exposure directly after application resulted in 0.010 mg a.i./kg bw/day for high crops (with gloves, work clothes like long-sleeved shirt and long trousers), and 0.004 mg/kg bw/day for low crops (with work clothes like long-sleeved shirt and long trousers).

The percentage of the AOEL (0.004 mg a.s./kg bw/day) accounted for is:

$$\%AOEL_{roses+apple} = 128\ \%$$

$$\%AOEL_{cabbage} = 51\ \%$$

Since this dermal exposure exceeds the AOEL of 0.004 mg a.i./kg*d for working activities in high crops, the estimation of the risk to workers might be refined by using compound-specific data on Foliar Dislodgeable Residues (FDR) or actual exposure measurements, the RMS is of the opinion that the work rate during re-entry in high crops should not be higher than 2 h/d.

In the absence of these data, the RMS proposes to consider the following options for reducing the risk for the workers

- to reduce the daily time of re-entry activities in high crops to a maximum of 2 hours/day, including this limit in the GAP;
- in alternative, to establish a period of inhibition for access to the area which allows enough time for the residues to decay to a safe level.

Available toxicological data relating to non active substances

All information relating to the composition of the product is confidential, therefore it is submitted separately

Summarising conclusions on human and animal health

Following its acute toxicity data Tamaron SL 200 is to be labeled as "toxic if swallowed", "harmful in contact with skin", "very toxic to aquatic organism" and "may cause long-term adverse effects in the aquatic environment". Tamaron SL 600 is to be labeled as "very toxic if swallowed" and "toxic in contact with skin", "very toxic to aquatic organism" and "may cause long-term adverse effects in the aquatic environment". Both products are non-irritating to skin; Tamaron SL200 is slightly irritant to the eye, Tamaron SL 600 is not irritant to the eye. Both are not skin sensitizers. When used according to the proposed GAP, methamidophos poses no acute or long-term dietary risk to humans with the use of WHO European diet.

Operator exposure remains within the AOEL only with the adoption of PPE and some restrictions in the GAPs.

The daily time of re-entry activities in high crops should be reduced to a maximum of 2 hours/day.

For accidental bystander exposure, preventive measures are recommended.

For residential bystander exposure, a buffer zone of 20 m. is recommended.

2.4 Residues

2.4.1 Definition of the residue relevant to the MRLs

Root and leaf treatment of different plants demonstrates that methamidophos is readily taken up by roots and leaves and transported apoplastic with the transpiration water towards the margin of the leaves. It appears that little if any amount of methamidophos entered a living cell or a vascular system but moved with the transpiration water in the cell wall system towards the leaf margin.

The results of the soil treatment show that soil-applied methamidophos was rapidly degraded in the soil and little of the radioactivity is taken up by the plant.

Radioactive residues in plants and tissue cultures are identified as desamino-methamidophos, S-methyl thiophosphoric acid, methanesulfonic acid and also as plant pigments, sugars, starch, cellulose, lipids, amino acids and proteins, indicating that the radioactivity is incorporated via carbon dioxide into natural plant constituents.

Loss of radioactivity in remarkable amounts is observed in several experiments performed. A possible explanation is the postulated tendency of the compound to decompose to the highly volatile methyl mercaptan.

It is postulated that the degradation in plants followed a hydrolytic route; hydrolysis first occurred to yield desamino-methamidophos, which is detected in many tissues investigated. Continued, though somewhat slower, hydrolysis of desamino-methamidophos apparently led to cleavage of CH_3S-P and CH_3O-P bonds yielding probably a conjugate of S-methyl thiophosphoric acid, methyl mercaptan and monomethyl phosphate as degradation products. Methyl mercaptan is likely as precursor of methanesulfonic acid, CO_2

and sulfate. CO_2 is incorporated into sugars, starch, cellulose, lipids, amino acids and proteins via photosynthesis.

Metabolism studies in rats and farm animals after oral or intravenous (rats only) administration of radioactively labelled methamidophos demonstrate a rapid absorption of the radioactivity, followed by fast distribution into organs and tissues.
More than half of the administered radioactivity is rapidly eliminated from the body. Urine and expired CO_2 are the major routes of elimination.
The radioactivity remaining in the animal after the initial rapid excretion is fairly evenly distributed throughout the body and incorporated into endogenous compounds (carbon-1 pool). This radioactivity is eliminated at a slower but constant rate in accordance with the natural turnover of these compounds.

In all test species, methamidophos is rapidly and thoroughly metabolised. Metabolism studies in animals show that methamidophos is rapidly degraded through deamination and/or demethylation. The first step is cleavage of either the P-O, P-N, or P-S bonds followed by demethylation.
In addition to unchanged methamidophos, the following major degradation products are found: desamino-methamidophos, monomethyl phosphate, S-methyl thiophosphoric acid, methyl phosphoramidate, S-methyl phosphoramidothioate, phosphoric acid and carbon dioxide. In plant metabolism studies methanesulfonic acid is identified as a degradation product of methamidphos. This metabolite is not detected in the rat. In plants methanesulfonic acid has to be regarded as an oxidation product of methyl mercaptan. It is highly likely that methyl mercaptan is also a degradation product of methamidophos in the animal. Studies concerning the metabolic behaviour of methyl mercaptan in-vivo (rats) and in-vitro (whole blood) show that this compound is rapidly oxidised to carbon dioxide and sulfate. Methanesulfonic acid is detected as an oxidation product of methyl mercaptan incubated with whole blood.

Conclusion

Plant: The metabolism studies in different crops and in two tissue cultures reveal that the metabolic patter is similar. The main metabolites (desamino-methamidophos, S-methyl thiophosphoric aci, methanesulfonic acid) found in plants is also detected in animal metabolism studies or can explained as intermediated in the degradation pathway . Consequently, the parent compound only has to be regarded as the residue of concern.

Animal: Metabolism studies in rats, lactating goats and laying hens reveal that methamidophos is rapidly excreted. Total ^{14}C residues in edible portions of goats and hens are very low and are likely to consist of natural products resulting from metabolism of methamidophos in the carbon-1 pool. Comparing results from metabolism studies in rats, goats and hens, the two metabolites identified in farm animals are the desamino-methamidophos and S-methyl phosphoramidothioate, which is also identified in the rat. Therefore it can be concluded that this metabolite is not of toxicological relevance. The parent compound only has to be regarded as the residue of concern.

2.4.2 Residue levels relevant to consumer safety

The notifier (a) submitted a full dossier regarding residues. The other notifier Sinon submitted only a few published scientific papers but no residue trials to support the intended uses.

To clarify the residue behaviour of methamidophos, numerous residue trials were conducted on different crops (see MRL proposals) to support the use of the 600 SL and 200 SL formulation in northern and southern Europe. As it is intended to harmonize the current GAP in EU member States in both regions, additional residue trials were carried out from 1995 to 1996 according to future GAP on apples, peaches, peppers, cucumbers, maize, potatoes, sugar beet, and tobacco.
Freezer storage stability studies demonstrate an adequate stability of methamidophos in a variety of crop and animal commodities during frozen storage for intervals ranging from 1 to 26 months. Methamidophos is determined to be stable for up to 26 months in various crops and up to 3 months in most animal commodities.

Processing studies were conducted with apple, peaches, tomatoes, peppers, cabbage, sugar beet, cotton seed, and soybeans.
In studies with peaches, residues were slightly reduced during washing of the fruit prior to processing and by processing into jam and preserves. Residues in peach juice are on average three times lower than in the fresh fruit. Processing studies with tomatoes show that methamidophos residues do not have a significant potential to concentrate in tomato juice, canned fruit and catsup. Methamidophos residues may have a potential to concentrate in puree, wet and dry pomace. Cooking has little impact on residues of methamidophos in tomatoes and savoy cabbage. Dehydration of peppers diminishes significantly methamidophos residues present in fresh peppers. During processing of oilseed crops, methamidophos residues do not concentrate in oil or soapstock. Residues do not concentrate in the meal and hulls of cottenseed, but they do concentrate in soybean hulls and in meal. There is no concentration of methamidophos residues during the processing of sugar beet.
Processing studies for potato, maize, cucumber, cauliflower/broccoli and kohlrabi were not submitted.
Animal transfer studies indicate that methamidophos is rapidly absorbed from the gastrointestinal tract and rapidly dispersed throughout the cattles and poultry. After daily oral administration of low levels of methamidophos in the diet to dairy and beef cattle as well as to laying hens, methamidophos residues could not be determined in milk, eggs, muscle, fat or other organs like heart, liver and kidneys. Even at much higher levels than the expected feeding levels, only small amounts of methamidophos residues could be determined in milk, eggs, organs and tissues. A few days after the last dosage fed to cattle, no residues of methamidophos were found in milk, organs and tissues.

Investigations on the behaviour in succeeding crops are not necessary due to the very rapid degradation of methamidophos in soil.
The ADI proposed by RMS in this monograph is 0.004 mg/kg bw.

The following results must be considered to be provisional because more supervised residue trials to support intended GAPs are needed for some crops, as are processing studies.

WHO established an Acceptable Daily Intake (ADI) of 0.004 mg/kg bw for methamidophos in 1990. The Theoretical Maximum Daily Intake (TMDI) of methamidophos has been calculated on the basis of the proposed EU MRLs and the WHO European diet (FAO/WHO, 1995). Following the 'Guidelines for

predicting dietary intake of pesticide residues' (WHO, 1989) the calculation results in about 0.10 mg/person/day or about 0.0017 mg/kg bw. This figure indicates that the TMDI corresponds to about 43% of the ADI for adults. For a female child using the German diet, the TMDI corresponds to about 94% of the ADI. TMDI calculation using the WHO Italian Diet resulted in a daily intake of 68% of the ADI, based on the UK Consumer Model the TMDI for the UK Diet was calculated to be 57% of the ADI for adults, 63% for children 170% for infants and 347% for toddlers.

The IEDI calculations showed that the intake of methamidophos was 1.69% of the established ADI of 0.004 mg/kg bw/day.

The NESTI calculations showed that the acute RfD (0.004 mg/kg bw/day) is exceeded for peppers and tomatoes for adults, and for apple, pear, peach, nectarine, pepper, tomatoes for toddlers.

A probabilistic approach based on the Monte Carlo technique indicates that the daily acute intake is below the aRfD at the 99.9th percentile with 67% of the aRfD for toddlers and 33.0% of the aRfD for adults.

Method used	Intake		% of ADI
	TMDI (mg/person/day)	(mg/kg/day)	
WHO Guidelines (1989) European diet - 60 kg bw	0.101959	0.00170	42
German BBA guidelines Part IV, 3-7 (1993), female child, 13.5 kg body weight	0.050800	0.00376	94

2.4.3 Residues relevant to worker safety

The residue relevant to worker safety is only represented by methamidophos.

2.4.4 Compliance with existing MRLs and/or proposed MRLs

The proposals for MRLs are made on the basis of the anticipated harmonised use patterns for northern and southern Europe. In the following table the proposed and established EU MRLs (93/57/EEC and 93/58/EEC) for methamidophos on products of animal origin and crops which will be maintained are summarised.

Summary of proposed and established EU MRLs for methamidophos

Group	proposed EU MRL (mg/kg)	established EU MRL (mg/kg)
Pome fruit	0.5	0.05[1)]
Stone fruit Peaches (incl. nectarines) Apricots	0.5	 0.05[1)] 0.1[1)]
Tomatoes	0.5	0.5
Peppers	2.0	0.01*[1)]
Cucumbers	0.5	1.0
Flowering brassica Cauliflower and Broccoli	0.01	0.5[1)]
Head cabbage	0.1	0.5
Kohlrabi	0.01*	0.01*
Cotton seed Soybeans	0.2 0.2	0.1 0.01*
Potatoes	0.01*	0.01*
Cereals Maize	 0.01*	0.01*
Sugar beet	0.01*	not established
Tobacco	25 (green leaves) 25 (dried leaves)	not established
Products of animal origin (incl. milk and eggs)	0.01*	0.01*

* indicates lower limit of analytical determination
** Council Directives 93/57/EEC and/or 93/58/EEC

2.5 Fate and distribution in the environment

2.5.1 Definition of the residues relevant to the environment

Methamidophos is degraded very rapidly in soil, natural water and in the air. The degradation in the soil is enhanced under field conditions. This very rapid degradation results in a very low leaching potential of methamidophos from the soil and indicates that no persistence or accumulation is expected to take place in the aquatic environment or in the atomsphere. Member States have to take into account that some areas in their country may happen to be vulnerable to groundwater leaching according to geological setting, type of crop and application rate.

Conclusion:

As methamidophos is rapidly degraded in the environment, the parent compound is of concern only for a short period after application. Metabolites from the degradation of methamidophos are not considered to be relevant to the environment.

2.5.2 Fate and behaviour in soil

It can be concluded that methamidophos is degraded very rapidly in soil. By the cleavage of the P-O bond S-methyl phosphoramidate *(M05)* was formed as a major degradation product. Cleavage of the P-N bond produced desamino-methamidophos *(M01)* as a minor metabolite. Both metabolites (*M01* and *M05*) in turn degraded rapidly under aerobic conditions to CO_2, the principal degradation product. In addition volatile sulphur compounds leading to dimethyl disulphide *(M10)* were formed.

The metabolite S-methyl phosphoramidothioate *(M05)* was also rapidly formed under anaerobic conditions and seemed to be stable. Formation of methane and also of volatile sulphur compounds under these conditions can be expected.

Results of soil photolysis studies showed that methamidophos degraded more quickly under irradiation than in the dark. The major degradation product was S-methyl phosphoramidothioate *(M05)*.

The half-lives under laboratory conditions range between 14 hours and 6 days. Under field conditions the degradation of methamidophos is even faster. Because of this rapid degradation in all trials the half-lives of methamidophos can not be calculated. They are estimated to be less than 2 days in the trials conducted in Germany and less than 1 day in an US trial.

Half-life of methamidophos in soil

Laboratory	14 hours - 6 days
Field	< 2 days

Based on adsorption, soil thin-layer chromatography, and column leaching studies, methamidophos can be classified as mobile in soil. However, the results from the metabolism, aged leaching, and field studies indicate that methamidophos degrades very rapidly. Part of the remaining radioactivity is bound to soil, which further decreases the amount of a.i. and/or metabolites, available for leaching. In an aged leaching

study only about 1% of the radioactivity originally applied to soil was found in the leachate. The low leaching potential is also confirmed by PEC_{gw} (PELMO) calculation and by field studies where methamidophos residues were not detected below 30.5 cm soil depth at a limit of detection of 0.01 mg/kg.

PEC in soil

Crop	Soil Coverage %	Application rate (a.i.)		Portion of a.i. reaching the soil		Initial PECs (mg a.i./kg d.w. soil) related to 5 cm soil depth
		kg/ha	mg/m²	kg/ha	mg/m²	
Field Crops	50	0.8	80	0.4	40	0.53
Orchard Crops	50	1.2	120	0.6	60	0.80
		0.5	50	0.25	25	0.33
Ornamentals	50	1.2	120	0.6	60	0.80
		0.4	40	0.2	20	0.27
Vegetables	50	1.2	120	0.6	60	0.80
		0.5	50	0.25	25	0.33

Longer term predicted environmental concentrations (PEC_l) were calculated as time-weighted average concentrations using the following formula:

$$PEC_l = PEC_i(DT_{50}/t_l(\ln 2))(1-e^{(-t_l(\ln 2)/DT_{50})})$$

where PEC_l = time-weighted average concentration, PEC_i = initial concentration, DT_{50} = half-life, and t_l = appropriate time period. This calculation assumes first-order kinetics for dissipation of methamidophos. A measured half-life for soil dissipation of methamidophos of 2 days. A scenario for multiple application has been evaluated.

Time course of the PEC_l for methamidophos in soil

Day	Actual concentration (% of initial)	Time weighted average (% of initial)
0	100	100
1	70.7	84.5
2	50	72.1
4	25	54.1
7	8.8	37.6
28	0.0061	10.3
50	0	5.8
100	0	2.9

The highest predicted concentration is 0.8 mg/kg dry weight soil. As methamidophos is not persistent, prolonged environmental exposure does not have to be expected.

2.5.3 Fate and behaviour in water

Surface water

In sterile buffer solutions at pH 7 the half-lives of methamidophos ranged between 5 and 27 days. Photolysis may contribute to the degradation of methamidophos in water. However, in natural water methamidophos is degraded much more rapidly.

The degradation of methamidophos was investigated under aerobic aquatic conditions using two water/sediment systems. The concentration of methamidophos in both, the surface water and the sediment, decreases rapidly. The half-lives for the total system (including water and sediment) are 4.1 and 5.8 days, respectively. DT_{50}-values calculated solely for the dissipation from the water phase are 4.0 and 7.8 days, respectively. After an incubation period of 32 days, only about 1% of the applied radioactivity in the surface water and sediment of both systems represents the parent compound. The largest amount of active ingredient added to the test systems is completely degraded to CO_2 as the end product of the mineralization process. After an incubation period of 60 days in both systems about 66% of the applied radioactivity are detected as CO_2. In the course of the metabolization of methamidophos small amounts of several metabolites are detected in water. No metabolite ever reaches an amount of 10% of the applied dose.

Longer term predicted environmental concentrations (PEC_i), used for comparison to longer-term aquatic continuous exposure studies, were calculated as time-weighted average concentrations using the same formula of soil PEC. A measured half-life for aquatic dissipation of methamidophos of 5.8 days was used for these calculations.

PEC_i (initial) in water, ground application

Crop	Distance (m)	Drift	Application rate (a.i.)		Portion of drift (a.i.)		PECsw i (µg a.i./L) water depth 30 cm
			kg/ha	mg/m²	kg/ha	mg/m²	
Field Crops	1	4%	0.8	80	0.032	3.2	10.7
Orchard Crops	3	29.6	1.2	120	0.3552	35.52	118
Early growth stage			0.5	50	0.148	14.8	49.3
Orchard Crops	3	15.5%	1.2	120	0.186	18.6	62
Late growth stage			0.5	50	0.0775	7.75	25.8
Ornamentals	10	1.5%	1.2	120	0.018	1.8	1.8
			0.4	40	0.006	0.6	0.6
Vegetables	5	12.5%	1.2*	120	0.15	15	50
			0.5	50	0.0625	6.25	20.8

* tomatoes only

There is no potential for persistence or accumulation of methamidophos or its metabolites in the aquatic environment as shown in the table below. Residues of methamidophos reaching aquatic systems are expected to be readily eliminated from the water.

Time course of PEC_{sw} for methamidophos in water

Day	Actual concentration (% of initial)	Time weighted average (% of initial)
0	100	100
1	88.74	94.26
2	78.74	88.95
4	62.00	79.49
5	55.02	75.28
7	43.32	67.75
14	18.77	48.55
21	8.13	36.61
28	3.52	28.83
42	0.66	19.79
60	0.08	13.94
84	0.00	9.96
120	0.00	6.97

Groundwater

The behaviour of methamidophos in soil and its potential environmental concentration in groundwater were calculated by computer modelling with the program PELMO. Half-life data from methamidophos degradation in soil and adsorption coefficients of two soils were used as input data. To ensure a conservative estimate, worst case conditions were used as input for the calculation.

The highest amount of the applied active ingredient is used in potatoes up to 4.08 kg a.i/ha/year (2×0.6, 3×0.48 and 2×0.72 kg a.i./ha). For the scenario the weather data from Hamburg (1961) were used and a 10 year period of continuous application of the active ingredient was assumed. As soil scenario a loamy sand was used. The results show that even under combination of worst case assumptions for soil, climate, degradation in soil and adsorption the predicted concentrations of methamidophos in ground water, which is assumed to be present already at a depth of 110 cm, are significantly below 0.1 µg/l. This indicates that - in spite of the very low adsorption - under the above mentioned boundary conditions no entry of methamidophos into deeper soil layers or into groundwater is to be expected, which is a consequence of the very rapid degradation in soil. The low potential of groundwater contamination by methamidophos is also confirmed by the aged leaching study with a sandy loam.

A report from Maine refers of some superficial wells contaminated by methamidophos in areas cultivated with potatoes. Sampling locations were chosen to provide information on pesticide concentrations in various types of aquifers, as well as to cover different agricultural areas of the State. Only wells adjacent to fields where pesticides are used where selected in order to consider the worst case situations. These areas were intensely farmed ones located in the most vulnerable areas for groundwater: sand, gravel deposits, water from till and bedrock fractures. However, due to all the information provided by the applicant, the RMS does not consider groundwater as a compartment at risk. Member States have to take into account that some areas in their country may happen to be vulnerable to groundwater leaching according to geological setting, type of crop and application rate.

2.5.4 Fate and distribution in air

The calculated half-life of methamidophos in air is 0.578 days and a value of 0.838 day for the chemical lifetime of methamidophos in the troposphere. Because of the short lifetime of methamidophos in air, methamidophos is unlikely to be transported in the gaseous phase over large distances or to accumulate in the air. On account of the relatively low trend to volatilise combined with the short life of methamidophos in air, an accumulation in the atmosphere and consequently a lasting contamination due to dry or wet deposition is not to be expected.

2.6 Effects on non-target species

2.6.1 Effects on terrestrial vertebrates

Birds

As for risk assessment the assumptions were:

- The estimation of the theoretically expected exposure in potential feed for birds is made according to Hoerger & Kenaga (1972) and considering the maximum application rate of 1.2 kg a.i./ha

- It is assumed, as a worst case, that birds feed exclusively on contaminated food, composed by insects (small + large), seed, grass, leaves fruit. Small birds have a daily feed demand of 30% of their body and large birds 10% of their body weight.

- The most sensitive species, Bobwhite quail and Junco hyemalis, have been used to calculate worst case TER values.

- A refined short and long term risk has been assessed assuming a TWA residue for Methamidophos in green mass of 64.21% (after 5 days) and 4.33% (after 120 day) of the typical initial residue estimated. Those percentages have been estimated considering a mean half-life of 3. 6 and the measured concentrations in cabbage.

The acute oral and dietary toxicity studies show that Methamidophos is highly toxic to birds Bobwhite quail (LD_{50} 10.1 mg a.i/kg b. w; LC_{50} 42 mg a.i /kg diet) and Junco hyemalis (LD_{50} 8 mg a.i/kg b. w.), the most sensitive species. Methamidophos presents also a significant reproductive toxicity to Bobwhite quail at 15 ppm, with a NOEC at 3 ppm.

The TER values show a potential high risk of Methamidophos for birds, both on acute and chronic conditions.

Acute and short term TERs: from 0.25 to 67.

Short term TERs with twa PEC: from 0.5 to 42

Long-term TERs: from 0.02 to 2

Long term TERs with twa PEC: from 0.5 to 44

Several estimated acute and oral short term TERs are below the trigger value 10 of Annex VI and all the long term TERs are below the trigger value 5 of Annex VI.
The short-term and long term risk (except for frugivorous birds) is still observed when the estimated theoretical exposures are corrected taking into account degradation.

In conclusion, TERs have shown an unacceptable risk for birds. However, feeding studies indicate an anti-feedant effect of the a.i. to birds and the results, obtained from a simulated field exposure study, show that sublethal effects (e.g. ChE inhibition), if they occur, are rapidly reversible.
Moreover, over the past 25 years, no deaths of birds were reported due to ingestion of Methamidophos in the crops.
Plant metabolism studies did not show that any risk from poisoning by metabolites is to be expected.
Due to the lack of a potential for bioaccumulation, secondary poisoning of birds by feeding on contaminated fish is not likely to occur.
It can be concluded therefore, that under practical conditions the risk to birds by Methamidophos as an insecticide in ornamentals, orchards, vegetables and field crops appears to be low.

Mammals
As for risk assessment the assumptions were:

- Mammals may be exposed to Methamidophos through ingestion of feed items treated with Tamaron 200 SL or 600 SL. The estimated exposures for various types of feed items are the same as the potential exposures estimated for birds.

- The estimation of the theoretically expected exposure in potential feed is made according to Hoerger & Kenaga (1972) and considering the maximum application rate of 1.2 kg a.i./ha.

- It is assumed, as a worst case, that mammals feed exclusively on contaminated food, composed by insects (small + large), seed, grass, leaves, fruit. Small mammals have a daily feed demand of 30% of their body and large mammals 10% of their body weight.

- The risk assessment for wild mammals is based on the most sensitive species:
  Acute: LD50 = 10 mg a.i./kg b.w rabbit.
  Short term: A 56 day sub-chronic study with Methamidophos (77.6% as.i.) on rats resulted in a NOEL: 0.5 mg a.i./kg diet.
  Chronic: A 2 generation chronic study with Methamidophos on rats revealed a NOEC of 10 and a LOEC of 33 mg a.i./kg diet.
- A refined short and long term risk has been made assuming a TWA residue for Methamidophos in green mass of 8.66% (after 56 days) and 4.33% (after 120 days) of the typical initial residue estimated. Those percentages have been estimated considering a mean half-life of 3. 6 and measured concentrations in cabbage.

Acute TERs: from 0.25 to 64.

Short term TERs: from 0.004 to 0.32

Short term TERs with twa PEC: from 0.04 to 3.7

Long term TERs: from 0.07 to 6.41.

Long term TERs with twa PEC: from 6.21 to 148

Both acute risk assessment (except for mammals that feed on fruit) and short-term risk assessment for mammals has resulted in TER values below the trigger 10 of Annex VI. Long term risk assessment has resulted in TER values below the trigger value 5 of Annex VI (except for eating fruit mammals).

Therefore it can be concluded that, in a worst case, Methamidophos poses a high potential acute, suchronic and chronic risk for mammals.

The short term risk for mammals is still observed when the estimated theoretical exposures are correct by degradation, while the long term TERs calculated with a twa – residues have shown an acceptable risk for mammals.

2.6.2 Aquatic organisms

As for risk assessment the assumptions were:

- Risk assessment has been based on both the most sensitive end-points listed below and PECsw calculated for the target crops at different distances. Initial PECssw for water range from 0.6 to 118 µg a.i./l and are the same for all aquatic organisms.

Test Species	Test System	Duration of exposure	Results (mg/l)	References
Oncorhynchus mykiss	acute toxicity	96h	LC_{50}: 40.0	9.2.1.1
Oncorhynchus mykiss	early life stage	97d	NOEC: 2.15	9.2.2.1
Daphnia magna	acute toxicity	48h	EC_{50}: 0.27	9.2.6.1
Daphnia magna	chronic toxicity	21d	NOEC: 0.026	9.2.7.1
Scenedesmus subspicatus	growth inhibition	96h	EC_{50}: > 178	9.2.8.1

- The acute and chronic risk assessment was refined assuming:

for the Acute

- Initial PECsw;
- New drift tables (BBA);
- Different buffer zone;

for the Chronic

- 2 applications;
- PECtwa (59.3% of initial DT_{50} 5.8 d);
- New drift tables (BBA);
- Different buffer zone.

The short term TERs for fish range from approximately 339 to 66667; for daphnids range from 2 to 450; for green algae are calculated in a range of 1508 and 296667.
The short term TERs with different buffer zone and the new drift tables for daphnids range from 103.8 to 177.6

The long term TERs for fish range from approximately 18 to 1194; for daphnids range from 0.2 to 2.43
The long term TERs with twa PECsw, 2 applications and the new drift table for daphnids range from 10.1 to 35

Overall, it can be concluded, that Methamidophos is not hazardous to fish and algae (acute and chronic TERs are greater than the trigger values 100 and 10 of Annex VI). As expected for an insecticide, daphnia are much more sensitive both as acute and chronic risk. The most acute and long term TERs are above the trigger value 100 and 10 of Annex VI, and show that an unacceptable risk exists for aquatic invertebrates. The risk is still observed when a twa PECsw is applied. Only the introduction of specific buffer zones guarantees an acceptable risk (Table B.9.2.13-6/7, annex B) and could be useful to protect the aquatic organisms.
Due to the lack of bio-accumulation potential, Methamidophos will not bio-concentrate in fish.

2.6.3 Honey bees

No Hazard Quotients for honey bees have been calculated, because only higher tier studies have been provided.
From a cage field toxicity trial, toxicity to honey bees, due to Methamidophos, proved to be very high, but decreased rapidly.
Methamidophos 720 SL at 1.12 kg a.i./ha caused a reduction in bee visitation for 3 days and killed a moderately high number of bees for 1½ days. The overall effect was considered to be a high toxicity level to honeybees.
Methamidophos 720 SL at 0.56 kg a.i./ha caused a reduction in bee visitation for 2-3 days and killed a slightly higher number of bees than observed in water-treated plots for 1 day. The overall effect was considered to be a moderately low toxicity level on honeybees.
Methamidophos should not be used during the flowering.

2.6.4 Earthworms and other soil non-target organisms

As for risk assessment the assumptions were:

- LC_{50} for earthworms Eisenia foetida is 28.8 and 73 mg a.i/kg soil (tested as Tarmaron 600 Sl.).
- PECs estimated assuming that 50% of the application reaches the soil (range from 0.27 to 0.8 mg a.i./kg soil., depending on the application rate).

Acute TERs: from 36 to 270.

These values indicates that all estimated acute TERs are above the trigger value 10 of Annex VI.

A field test indicated that the earthworm populations were not negatively affected by 4-fold application rate (2 times 16 kg/ha) of Tamaron 600 SL, 6-8 weeks, 1/2 year and 1 year after the first application.
The results mentioned above together with a rapid degradation of Methamidophos in soil indicate that a negative impact on earthworms is not to be expected.
In conclusion a good margin of safety exists for earthworms.

2.6.5 Beneficial arthropods

No studies on the most sensitive species have been provided.
Laboratory testing with a formulated product was conducted for several strains of two species of predatory mites by spraying the product on glass plates at a dose equivalent to 110 g a.i./ha. All mites were fully susceptible to Tamaron.
Similarly, laboratory testing with the green lacewing was conducted by spraying glass plates with a formulated product at a dose equivalent to 180 g a.i./ha. One hundred percent mortality occurred in the treatment group.
In conclusion, Methamidophos is acutely toxic to a variety of beneficial arthropods. Since Methamidophos residues are short-lived, insects appear to be able to re-colonise treated fields shortly after the residues fall below the respective toxic thresholds. Long term effects are therefore not to be expected.

2.6.6 Soil microbial activity

The laboratory studies performed with Methamidophos as Tamaron 600 SL concerning the effects on soil micro-organism C- and N-cycle over a period of 28 days reveal that at the recommended application rates, Methamidophos does not have negative influence on microbial mineralization processes in field soils.

Due to the lack of bactericidal activity of Methamidophos, a risk to biological sewage treatment processes has not to be expected.

Summarising conclusions

Methamidophos shows a high potential risk for terrestrial vertebrates, although under practical conditions, the risk to birds appears to be low. Methamidophos is not hazardous to aquatic organisms, except for aquatic invertebrates. It does not accumulate in fish.
No Hazard Quotients for honeybees have been calculated, because only higher tier studies have been provided. From a cage field toxicity trial, toxicity to honey bees proved to be very high, but decreased rapidly few days after treatment.
Due to its rapid degradation, Methamidophos does not show a negative impact on earthworms. The risk for beneficial arthropods is high, even if they appear to be able to re-colonise treated fields shortly after the

residues fall below the respective toxic thresholds. However, as data provided are insufficient, further studies on beneficial arthropods are necessary. The risk for soil micro-organisms can be considered as negligible.

Overall conclusions

From the data submitted it may be concluded that use of plant protection products containing methamidophos in accordance with the principles of good agricultural practice is acceptable if certain restrictions to the use are applied.

Residues which occur in plants, animal tissue, soil or water as a consequence of use of methamidophos in accordance with the principles of good agricultural practice do not have unacceptable harmful effect on human health. The use of methamidophos poses an unacceptable risk for aquatic invertebrates if a buffer zones are not applied. It is toxic for artropods, and for terrestrial vertebrates. Other unacceptable influences on the environment are not expected.

Appendix 1 Standard terms and abbreviations

Technical Terms

A	ampere
ACh	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADP	adenosine diphosphate
AE	acid equivalent
AFID	alkali flame-ionization detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD50	approximate median lethal dose, 50%
ALT	alanine aminotransferase (SGPT)
AOEL	acceptable operator exposure level
AMD	automatic multiple development
ANOVA	analysis of variance
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathie
BSP	bromosulfophthalein
Bt	bacillus thuringiensis
Bti	bacillus thuringiensis israelensis
Btk	bacillus thuringiensis kurstaki
Btt	bacillus thuringiensis tenebrionis
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10 -2)
°C	degree Celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application
cDNA	complementary DNA
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre

CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
cv	coefficient of variation
Cv	ceiling value
CXL	Codex Maximum Residue Limit (Codex MRL)
d	day
DES	diethylstilboestrol
DFR	dislodgeable foliar residue
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic Acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days pot inoculation
DRES	dietary risk evaluation system
DT50	period required for 50 percent dissipation (define method of estimation)
DT90	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC50	median effective concentration
ECD	electron capture detector
ECU	European currency unit
ED50	median effective dose
EDI	estimated daily intake
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EPMA	electron probe micro analysis
ERC	environmentally relevant concentration
ERL	extraneous residue limit
F	field
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FIA	fluorescence immuno assay
FID	flame ionization detector
FOB	functional observation battery
fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram
G	glasshouse
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionization detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase

GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPPP	good plant protection practice
GPS	global positioning system
GSH	glutathion
GV	granulosevirus
h	hour(s)
H	Henry's Law constant (calculated as a unitless value) (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionization detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography - mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
H_S	Shannon-Weaver index
Ht	haematocrit
I	indoor
I_{50}	inhibitory dose, 50%
IC_{50}	median immobilization concentration or median inhibitory concentration 6
ICM	integrated crop management
ID	ionization detector
IEDI	international estimated daily intake
IGR	nsect growth regulator
im	intramuscular
inh	inhalation
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
iv	intravenous
IVF	*in vitro* fertilization
k	kilo
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H) 6
Kads	adsorption constant
Kdes	apparent desorption coefficient
Koc	organic carbon adsorption coefficient
Kom	organic matter adsorption coefficient
kg	kilogram

L	litre
LAN	local area network
LASER	light amplification by stimulated emission of radiation
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography- mass spectrometry
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LC_{Lo}	lethal concentration low
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LD_{Lo}	lethal dose low
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
µm	micrometer (micron)
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram
MHC	moisture holding capacity
min	minute(s)
mL	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
mo	month(s)
mol	Mole(s)
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
MRL	maximum residue level or limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
n	normal (defining isomeric configuration) or number of observations 6
NAEL	no adverse effect level
nd	not detected

NEDI	national estimated daily intake
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometer
NMR	nuclear magnetic resonance
no	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	zone-depleting substances
OM	organic matter content
op	organophosphorous pesticide
Pa	pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the dissociation constant)
PNEC	predicted no effect concentration
po	by mouth
Pow	partition coefficient between n-octanol and water
POP	persistent organic pollutants
ppb	parts per billion (10 -9)
PPE	personal protective equipment
ppm	parts per million (10 -6)
ppp	plant protection product
ppq	parts per quadrillion (10 -24)
ppt	parts per trillion (10 -12)
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit

PT	prothrombin time
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RBC	red blood cell
REI	restricted entry interval
Rf	retardation factor
RfD r	eference dose
RH	relative humidity
RL_{50}	median residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	*rotations per minute*
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RSD	relative standard deviation
s	second
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SD	standard deviation
se	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
sq	square
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STMR	supervised trials median residue
t	tonne (metric ton)
$t_{½}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TC_{Lo}	toxic concentration, low
TID	thermionic detector, alkali flame detector
TD_{Lo}	toxic dose low

TDR	time domain reflectrometry
TER	toxicity exposure ration
TER_I	toxicity exposure ration for initial exposure
TER_{ST}	toxicity exposure ration following repeated exposure
TER_{LT}	toxicity exposure ration following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
TIm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TOC	total organic carbon
Tremcard	Transport emergency card
tRNA	transfer ribonucleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
ww	wet weight
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Organisations and Publications

ACPA	American Crop Protection Association
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
CA	Chemical Abstracts
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles

CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CIPAC	Collaborative International Pesticides Analytical Council Ltd
COREPER	Comite des Representants Permanents
EC	European Commission
ECB	European Chemical Bureau
ECCA	European Crop Care Association
ECDIN	Environmental Chemicals Data and Information Network of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECLO	Emergency Centre for Locust Operations
ECMWF	European Centre for Medium Range Weather Forecasting
ECPA	European Crop Protection Association
EDEXIM	European Database on Export and Import of Dangerous Chemicals
EHC (number)	Environmental Health Criteria (number)
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organization
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques (now known as GCPF)
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GIEWS	Global Information and Early Warning System for Food and Agriculture
GRIN	Germplasm Resources Information Network
HRAC	Herbicide Resistance Action Committee
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
IBT	Industrial Bio-Test Laboratories
ICBB	International Commission of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commission for Plant-Bee Relationships
ILO	International Labour Organization
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety

IRAC	Insecticide Resistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Organization
ISO	International Organization for Standardization
IUPAC I	nternational Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
NATO	North Atlantic Treaty Organisation
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Centre for Toxicological Research (USA)
NGO	non-governmental organization
NTP	National Toxicology Programme (USA)
OECD	Organization for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
PAN	Pesticide Action Network
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCPH	Standing Committee on Plant Health
SETAC	Society of Environmental Toxicology and Chemistry
SI	Systeme International d'Unites
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UN	United Nations
UNEP	United Nations Environment Programme
WCDP	World Climate Data Programme
WCP	World Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organization
WTO	World Trade Organization
WWF	World Wildlife Fund

Appendix 2 Specific terms and abbreviations

Preparation (Formulation) Types and Codes*

Code	Description	Definition
AB	Grain bait	Special forms of bait.
AE	Aerosol dispenser	A container-held preparation which is dispersed generally by a propellant as fine droplets/particles upon actuation of a valve.
AL	Other liquids to be applied undiluted	Self defining.
BB	Block baits	Special forms of bait.
BR	Briquette	Solid block designed for controlled release of active ingredient into water.
CB	Bait concentrate	A solid or liquid intended for dilution before use as a bait.
CG	Encapsulated granule	A granule with a protective or release controlling coating.
CS	Capsule suspension	A stable suspension of capsules in a fluid normally intended for dilution with water before use.
DC	Dispersible concentrate	A liquid homogeneous preparation to be applied as a solid dispersion after dilution in water.
DP	Dustable powder	A free-flowing powder suitable for dusting.
DS	Powder for dry seed treatment	A powder for application in the dry state directly to seed.
EC	Emulsifiable concentrate	A liquid, homogenous preparation to be applied as an emulsion after dilution in water.
ED	Electrochargeable liquid	Special liquid preparation for electrostatic (electrodynamic) spraying.
EO	Emulsion, water in oil	A fluid, heterogeneous preparation consisting of a dispersion of fine globules of pesticide in water in a continuous organic liquid phase.
ES	Emulsion for seed treatment	A stable emulsion for application to the seed either directly or after dilution.
EW	Emulsion, oil in water	A fluid, heterogeneous preparation consisting of a dispersion of fine globules of pesticide in an organic liquid in a continuous water phase.
FD	Smoke tin	Special form of smoke generator.
FG	Fine granule	A granule in the particle size range from 300 to 2500 µ.
FK	Smoke candle	A smoke generator in the form of a candle.
FP	Smoke cartridge	Special form of smoke generator.
FR	Smoke rodlet	Special form of smoke generator.
FS	Flowable concentrate for seed treatment	A stable suspension for application to the seed either directly or after dilution.
FT	Smoke tablet	Special form of smoke generator.
FU	Smoke generator	A combustible preparation generally solid, which upon ignition releases the active substances in the form of a smoke.
FW	Smoke pellet	Special form of smoke generator.
GA	Gas	A gas packed in pressure bottle or pressure tank.
GB	Granular bait	Special forms of bait.
GE	Gas generating product	A preparation which generates a gas by chemical reaction.
GG	Macrogranule	A granule in the particle size range from 2000 to 6000 µ.
GP	Flo-dust	Very fine dustable powder for pneumatic application in glass-houses.
GR	Granule	A free-flowing solid preparation of a defined granule size range ready for use.
GS	Grease	Very viscous preparation based on oil or fat.
HN	Hot fogging concentrate	A preparation suitable for application by fogging equipment either directly or after dilution.
KN	Cold fogging concentrate	A preparation suitable for application by cold fogging equipment, either directly or after dilution.
LA	Lacquer	A solvent based film-forming preparation.
LS	Solution for seed treatment	A solution for application to the seed either directly or after dilution.
MG	Microgranule	A granule in the particle size range from 100 to 600 µ.

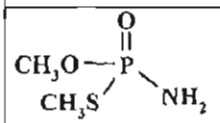
OF	Oil miscible flowable (=oil active substances in a miscible suspension)	A stable suspension of concentrate fluid intended for dilution in an organic liquid before use.
OL	Oil miscible liquid	A liquid, homogenous preparation to be applied as a homogenous liquid after dilution in an organic liquid.
OP	Oil dispersible powder	A powder preparation to be applied as a suspension after dispersion in an organic liquid.
PA	Paste	A water based film forming preparation.
PB	Plate bait	Special forms of bait.
PC	Gel or paste concentrate	A solid preparation to be applied as a gel or a paste after dilution with water.
PR	Plant rodlet	A small rodlet, usually a few centimetres in length and a few millimetres in diameter containing active substance.
PS	Seed coated with a pesticide	Self defining.
RB	Bait (ready for use)	A preparation designed to attract and be eaten by the target species.
SB	Scrap bait	Special forms of bait.
SC	Suspension concentrate	A stable suspension of active substance(s) in a fluid (= flowable concentrate) intended for dilution with water before use.
SE	Suspo-emulsion	A fluid, heterogeneous preparation consisting of a stable dispersion of active substance(s) in the form of solid particles and of fine globules in a continuous water phase.
SG	Water soluble granules	A preparation consisting of granules to be applied as a true solution of active substance after dissolution in water but may contain insoluble inert ingredients.
SL	Soluble concentrate	A liquid homogenous preparation to be applied as a true solution of the active substance after dilution with water.
SO	Spreading oil	A preparation designed to form a surface layer on application to water.
SP	Water soluble powder	A powder preparation to be applied as a true solution of the active substance after solution in water but which may contain insoluble inert ingredients.
SS	Water soluble powder for seed treatment	A powder to be dissolved in water before application to the seed.
SU	Ultra low volume (ULV) suspension	A suspension ready for use through ULV equipment.
TB	Tablet	Solid preparation in the form of small, flat plates for dissolution in water.
TP	Tracking powder	A rodenticidal contact preparation in powder form.
UL	Ultra low volume (ULV) liquid	A homogenous liquid ready for use through ULV equipment.
VP	Vapour releasing product	A preparation containing one or more volatile ingredients, the vapours of which are released into the air. Evaporation rate normally is controlled by using suitable preparations and/or dispensers.
WG	Water dispersible	A preparation granule consisting of granules to be applied after disin tegration and dispersion in water.
WP	Wettable powder	A powder preparation to be applied as a suspension after dispersion in water.
WS	Water dispersible powder for slurry seed treatment	A powder to be dispersed at high concentration in water before application as a slurry to the seed.
XX	Others	

Appendix 3 List of endpoints

Chapter 2.1: Identity, Physical and Chemical Properties, Details of Uses, Further Information, and Proposed Classification and Labelling

Active substance (ISO Common Name)	Methamidophos
Function (*e.g.* fungicide)	Insecticide
Rapporteur Member State	Italy

Identity (Annex IIA, Point 1)

Chemical name (IUPAC)	O,S-dimethyl phosphoramidothioate
Chemical name (CA)	O,S-dimethyl phosphoramidothioate
CIPAC N°	355
CAS N°	10265-92-6
EEC N° (EINECS or ELINCS)	015-095-00-4 (233-606-0)
FAO Specification (including year of publication)	FAO Provisional Specification 355/TC/S/P (1992). The methamidophos content shall be declared (not less than 680 g/kg) and, when determined, the content obtained shall not differ from that declared by more than ± 25 g/kg.
Minimum purity of the active substance as manufactured (g/kg)	CONFIDENTIAL
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	None
Molecular formula	$C_2H_8NO_2PS$
Molecular mass	141.1
Structural formula	

[15] *Other end points will be relevant in particular cases - decisions as to the additional end points to be included can only be made on a case by case basis.*

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity)	(a) Testmaterial: batch-no.: 920914ELB01 (purity 99.5%) Results: 45 °C (b) Testmaterial: Waxy solid as manufactured Results: 45 °C
Boiling point (state purity)	Not measurable, decomposition above 160°C
Temperature of decomposition	(a) Testmaterial: batch-no.: APF06028650 (purity 99.7%) Results: DSC-measurement (closed ampoule):exothermic decompositionbetween 160°C and 215°C TGA-measurement (open crucible):weight loss due to decomposition between 100°C and 220°C (b) Methamidophos is known to be stable at ambient temperature but decomposes on heating without boiling (no test)
Appearance (state purity)	(a) Pure active ingredient: crystals Active substance as manufactured: liquid or crystal slurry (b) Pure active ingredient: crystals Active substance as manufactured: waxy solid
Relative density (state purity)	(a) Testmaterial: batch-no.: 920914ELB01 (purity 99.5%) Results: 1.27 g/cm³ at 20 °C (b) Testmaterial: Waxy solid as manufactured Results: 1.333 g/cm³ at 20 °C (not acceptable)
Surface tension	(a) Testmaterial: batch-no.: 920914ELB01 (purity 99.5%) Results: 65 mN/m shows aqueous solutions of Methamidophos to be non-surface active. (b) Not determined
Vapour pressure (in Pa, state temperature)	(a) Testmaterial: batch-no.: 870716ELB05 (purity 99.5%) Results: 2.3×10^{-5} h Pa at 20°C (b) Not available
Henry's law constant (Pa m^3 mol^{-1})	(a) H < 1.6×10^{-6} Pa x m^3 x mol^{-1} (b) Not available
Solubility in water (g/l or mg/l, state temperature)	(a) Testmaterial: batch-no.: APF09028750 (purity 99.5%) Results: > 200 g/l at 20 °C. (b) Testmaterial: Waxy solid as manufactured Results: > 2 kg/l at 20 °C.. (not acceptable)
Solubility in organic solvents (g/l or mg/l, state temperature)	(a) Testmaterial: batch-no.: KRJ031180 (purity 99.5%) not on active substance as manufactured. Results: n-Hexane < 1 g/l at 20 °C Toluene 2 - 5 g/l at 20 °C Dichloromethane > 200 g/l at 20 °C 2 - Propanol > 200 g/l at 20 °C Acetone > 200 g/l at 20 °C Dimethylformamide > 200 g/l at 20 °C (b) Not available
Partition co-efficient (log P_{ow}) (state pH and temperature)	(a) Testmaterial: batch-no.: APF21088500 (purity 99.7%) Results: logPow = -0.80 at 20 °C (b) Testmaterial: Waxy solid as manufactured Results: logPow = 0.32 at 20 °C (Not acceptable)
Hydrolytic stability (DT_{50}) (state pH and temperature)	(a) Testmaterial: batch-no.: KRJ230184 (purity 99.3%) Results: Half-life of methamidophos in aqueous buffer at 22°C (*extrapolated*) pH 4 660 d pH 7 5 d pH 9 3 d Testmaterial: [S-methyl-^{14}C]-methamidophos (radiochemical purity: >98%; specificactivity: 25.7 mCi/mmol) Results: Half-life of methamidophos in aqueous buffer at 25°C (extrapolated) pH 5 309d pH 7 27d pH 9 3d Hydrolysis products; methyldisulfanylmethane, thiophosphoric acid, O,S-dimethyl ester, thiophosphoramidic acid, S-methyl

	ester. (b) Not determined
Dissociation constant	Methamidophos has neither basic nor acidic properties in water. Thus it is not possible to determine a pK value
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	(a) max 217.4 nm (b) Not available
Photostability (DT_{50}) (aqueous, sunlight, state pH)	(a) Testmaterial: [S-methyl-^{14}C]-methamidophos (radiochemical purity: >98%; specific activity: 25.7 mCi/mmol) Results: Photodecomposition was first-order and yielded half-life values of 37 days in continuous simulated sunlight and 90 days under natural sunlight (Kansas USA, latitude 38°49', longitude 94°40', 320 m above sea level). The differences between the two systems were therefore largely attributable to the period of irradiation (24-hour vs. 12-hour days). In both systems, the primary photolysis products were desmethyl methamidophos and deamidated methamidophos. An additional unknown photolysis product was observed in both systems, but did not exceed 2% of the applied radioactivity. (b) Not determined
Quantum yield of direct phototransformation in water at λ > 290 nm	(a) Testmaterial: batch-no.: 900208ELB01 (purity 99.0%) Results: The UV absorption data showed that methamidophos in aqueous solution does not absorb any light at wavelenghts above about 250 nm. The determination of the quantum yield in order to estimate the environmental half-life makes no sense in this case, because no contribution of the direct photodegradation to the overall elimination of methamidophos in the environment is to be expected (b) Not available
Flammability	(a) Testmaterial: Active substance as manufactured - (batch no.: 278567036/1, purity 75.4 %) Results: Tamaron TA is not highly flammable in the sense of EU Guideline A.10. Testmaterial: Active substance as manufactured - (batch no.: 278567036/1, purity 75.4 %) Results: Ignition point: 320 °C (b) Not available
Explosive properties	(a) Testmaterial: Active substance as manufactured - (batch no.: 278567036/1, purity 75.4 %) Results: Tamaron TA is not explosive in the sense of EU Guideline A.14 (b) Methamidophos is combustible but not explosive. On combustion, methamidophos forms nitrogen, phosphorus and sulphur oxides (no test).

Summary of intended Uses

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Pome fruit	SMS	Tamaron SL 200 Tamaron SL 600	F	aphidina, lepidoptera,psyllidae, tetranychidae	SL	19.5% 600 g/L	High volume spraying	at infestation	1-2		0.06	830-200	0.5-1.2	21	
Peach incl. nectarines[1]	SMS	Tamaron SL 200 Tamaron SL 600	F	aleurodidae, aphidina, lepidoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-2		0.05	1000-1500	0.5-0.75	21	
Tomato	SMS	Tamaron SL 200 Tamaron SL 600	F/G	aleurodidae, aphidina, lepidoptera, thysanoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-3		0.06	800-2000	0.48-1.2	7	
Pepper, sweet	SMS	Tamaron SL 200 Tamaron SL 600	F/G	aphidina, lepidoptera, thysanoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-3		0.06	500-2000	0.3-1.2	7	
Cucumber	SMS	Tamaron SL 200 Tamaron SL 600	F/G	aleurodidae, aphidina, lepidoptera, thysanoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-3		0.06	500-2000	0.3-1.2	7	
Flowering brassica (Cauliflower/Broccoli)	NMS	Tamaron SL 200 Tamaron SL 600	F	aphidina, homoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-2		0.06	600	0.36	21	
Cabbage (red, white, Savoy)	NMS	Tamaron SL 200 Tamaron SL 600	F	aphidina, homoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-2		0.06	600	0.36	21	
Kohlrabi	NMS	Tamaron SL 200 Tamaron SL 600	F	aphidina, homoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-2		0.06	600	0.36	14	
Potatoes [2]	NMS	Tamaron SL	F	aphidina,	SL	19.5%	High volume	at infestation	1-7		0.18	270-400	0.49-0.72	21	

		200 Tamaron SL 600		coleoptera		600 g/L	spraying								
Potatoes	SMS	Tamaron SL 200 Tamaron SL 600	F	alcurodidae, aphidina, lepidoptera, thysanoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-3		0.09	350-700	0.315-63	21	
Maize / Corn	SMS	Tamaron SL 200 Tamaron SL 600	F	aleurodidae, aphidina, lepidoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-2		0.1	480-800	0.48-0.8	60	
Sugar and fodder beet	NMS + SMS	Tamaron SL 200 Tamaron SL 600	F	aphidina, diptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-2		0.125	280-400	0 35-0.5	28 beet, 90leaf silage [3]	
Tobacco [1]	SMS	Tamaron SL 200 Tamaron SL 600	F	aphidina, cicadina, thysanoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-2		0.075	600-1000	0.45-0.75	7/21	
Ornamental (incl. closed forest)	NMS + SMS	Tamaron SL 200 Tamaron SL 600	F/G	aleurodidae, aphidina, lepidoptera, tetranychidae, thysanoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	2-3		0.06	670-2000	0.4-1.2	n.a.	

1) For peaches and tobacco the proposed critical use patterns of the combination product Tamaron & Confidor has been included. This product is under development and not registered in EU Member States. PHIs of 21 days (peach) and 7 days (tobacco) are proposed. The registered uses of Tamaron require for peaches and tobacco a PHI of 21 days

2) The critical use pattern for potatoes in Germany covers the control of viruses transmitting aphids in seed potatoes (1-7 x 0.48 - 0.6 kg ai/ha)

3) Sugar beet leaves are not fed to cattle before 90 days after the last treatment because of the time needed for silage production

(a) For crop, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)

(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)

(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds

(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989

(f) All abbreviations used must be explained

(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench

(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated

(i) g/kg or g/l

(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(k) Indicate the minimum and maximum number of application possible under pratical conditions of use

(l) PHI - minimum pre-harvest interval

(m) Remarks may include: Extent of use/economic importance/restrictions

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	
with regard to toxicological data	T, R 21, R 25, S 28, S 36/37, S 45
with regard to fate and behaviour data	
with regard to ecotoxicological data	N, R 50, R 53

Chapter 2.2: Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (principle of method)	Routine analysis of technical batches includes the CIPAC method 355/TC/M3 for determination of the active ingredient content in the technical material and its solutions. The components are separated by HPLC with isocratic elution. The quantitative evaluation is done by comparing the HPLC peak areas with an external standard.
Impurities in technical as (principle of method)	The impurities [redacted] are determined in industrial product and in active ingredient presolutions by capillary gas chromatography with internal standard (CIPAC draft method 355/TC/M/4). [redacted]
Plant protection product (principle of method)	(a) CIPAC method 355/TC/M3. Reversed-phase HPLC of a sample solution with UV-detection and evaluation with external standard. (b) HPLC equipped with an RI detector has been used to identify a Tamaro 50% product. Separation was made on a 12 X1/4" O.D. precision bore stainless steel column packed with micro- Bondapak/n-C18. The eluting solvent was 10% (v/v) methanol in distilled water. Analytical range 400-800 ppm. GLP: No

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	**GLP**: No **Extraction**: acetone and water **Clean-up/devia.**: gel permeation chromatography mixture of cyclohexane and ethyl acetate as eluant. **Determination**: GC **LOQ**: 0.01 mg/kg **GLP**: No **Extraction**: ethyl acetate in the presence of anhydrous granular sodium sulfate. **Clean-up/devia.**: silica gel column. **Determination**: GC-TID. **LOQ**: - **GLP**: No **Extraction**: homogenized with acetone and sodium carbonate. **Clean-up/devia.**: Filtered, and sequentially partitioned with hexane, chloroform, and chloroform/acetone. **Determination**: GC-FID **LOQ**: 0.01 mg/kg **GLP**: No **Extraction**: ethyl acetate **Clean-up/devia.**: silica gel column **Determination**: GC-TID **LOQ**: 0.05 mg/kg **GLP**: No **Extraction**: sodium sulfate with ethyl acetate. **Clean-up/devia.**: silica gel column. **Determination**: GC-TID LOQ: 0.01 mg/kg **GLP**: No **Extraction**: acetone **Clean-up/devia.**: partitioned with methylene chloride/petroleumether to remove water. After adding NaCl to the water phase, this phase is again extracted with methylene chloride. **Determination**: GLC, using a KCE thermionic detector. **LOQ**: - **GLP**: No **Extraction**: acetone or acetone/water. **Clean-up/devia.**: silica gel column **Determination**: GC-FID **LOQ**: 0.005 mg/kg **GLP**: No **Extraction**: ethyl acetate and water (190:10). **Clean-up/devia.**: **Determination**: GC-FID

	LOQ: 0.01 mg/kg **GLP**: No **Extraction**: methanol:chloroform (1:1) **Clean-up/devia.**: silica gel column. **Determination**: GC-TID **LOQ**: 0.01 mg/kg **GLP**: Yes ***Extraction**: acetone or acetone/water.* **Clean-up/devia.**: Phase partition on an extraction column filled with diatomaceous earth. The column is prewashed with n-hexane, before methamidophos is eluted with a ethyl acetate/ethanol-mixture. The extract is again cleaned up on a silica gel column with dichloromethane/acetone. ***Determination**: GC-FPD* **LOQ**: 0.01 mg/kg, tobacco 0.05 mg/kg. **GLP**: No **Extraction**: different mixtures. **Clean-up/devia.**: gel permeation chromatography. **Determination**: GC-TID **LOQ**: 0.01 mg/kg **GLP**: No **Extraction**: ethyl acetate in the presence of anhydrous granular sodium sulfate. **Clean-up/devia.**: gel permeation chromatography. **Determination**: GC-TID or GC-FPD. **LOQ**: 0.01 mg/kg **GLP**: No **Extraction**: ethyl acetate in the presence of anhydrous granular sodium sulfate. **Clean-up/devia.**: After evaporation to dryness, the residues are redissolved in acetone. **Determination**: GC-FPD **LOQ**: 0.01 mg/kg
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	**GLP**: No Yes **Extraction**: milk, eggs and animal tissues are extracted with ethyl acetate. **Clean-up/devia.**: silica gel column. **Determination**: GC-FPD **LOQ**: 0.01 mg/kg **GLP**: No **Extraction**: Milk and bovine tissues are sequentially extracted with acetonitrile and Skellysolve B and milk is blended with acetone and sequentially partitioned with chloroform and Skellysolve B and acetonitrile **Clean-up/devia.**: silica gel column. **Determination**: GC-TID **LOQ**: 0.004 mg/kg (milk), 0.02 mg/kg (all other tissues).

	GLP: No **Extraction**: Milk was extracted with ethyl acetate. Urine was cleaned up on a silicic acid column, and methamidophos was eluted with 5% methanol in ethyl ether. All tissues (except liver) were extracted using the method described for oily crops. Liver was extracted with ethyl acetate. **Clean-up/devia.**: the ethyl acetate was evaporated off, and the residue was dissolved in acetonitrile and partitioned with hexane. **Determination**: **LOQ**: 0.005-0.01 mg/kg **GLP**: No **Extraction**: Trout samples, acetonitrile in the presence of anhydrous sodium sulphate in a mixer followed by filtration through glass fibre disks in a Buchner funnel. **Clean-up/devia.**: Residue disolved in ethyl acetate followed by hexane and passed through glass column containing a glass wool plug, sodium sulphate, 2:5 mixture of Nuchar C and Whatman CF-11, sodium sulphate, the glass wool plug and the eluate discarded and Methamidophos eluted from the column in ethyl acetate, **Determination**: GC-FPD **LOQ**: -
Soil (principle of method and LOQ)	**GLP**: No **Extraction**: acetone/water **Clean-up/devia.**: by phase partition against n-hexane **Determination**: GC-TID **LOQ**: 0.01 mg/kg **GLP**: No **Extraction**: chloroform/methanol using a Soxhlet extractor. **Clean-up/devia.**: washed with benzene and then extracted 3x with 120 ml of 2:1 chloroform:acetone after the addition of salt. **Determination**: GC-FID **LOQ**: 0.01 mg/kg (modified method) **GLP**: - **Extraction**: homogenised in acetonitrile; centrifugated and the supernatant filtered. The remaining sediment was soaked in acetonitrile, recentrifuged and the supernatant combined with that obtained previously. **Clean-up/devia.**: vacuum -concentrated and re-extracted in toluene, dehydrated with anhydrous sodium sulphate and filtered. **Determination**: not specified for methamidophos. **LOQ**: 30 pg/g dry wt.

Water (principle of method and LOQ)	**GLP**: No **Extraction**: extraction column filled with modified silica gel. **Clean-up/devia.**: **Determination**: GC-FPD **LOQ**: 0.1 µg/L **GLP**: No **Extraction**: After adding sodium chloride to the water sample methamidophos is extracted from these water samples by phase partition with ethyl acetate on diatomaceous earth **Clean-up/devia.**: **Determination**: GC-FPD **LOQ**: 0.2 µg/L **GLP**: No **Extraction**: Cold extraction of 1L sample with 50 ml of chloroform. **Clean-up/devia.**: chloroform layer was dried in a 10 cm column of anhydrous sodium sulphate (2x). **Determination**: GC-FPD **LOQ**: 0.01 µg/L
Air (principle of method and LOQ)	**GLP**: No Air is pumped through Tenax or XAD-2 adsorption tubes. The adsorbed methamidophos is extracted with n-butyl acetate and determined by gas chromatography using a nitrogen and phosphorous selective detector. **LOQ**: 0.0008 mg a.i./m^3
Body fluids and tissues (principle of method and LOQ)	In support diagnostic regimes the determination of acetylcholinesterase (AChE) in whole blood is used.

Chapter 2.3: Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism in mammals (Annex IIA, point 5.1)

Rate and extent of absorption :	At day 28 after intragastric administration 80-90% of methamidophos is excreted mainly via urine (60-70%) and via faeces.
Distribution :	Widely distributed
Potential for accumulation :	*No potential for accumulation*
Rate and extent of excretion :	50-60%, based on urinary excretion within 24 hours
Metabolism in animals :	Methamidophos is metabolised to several compounds: desamino-methamidophosm monomethyl phosphate, methylphosphoramidate, S-methylphosphoramidothioate and phosphoric acid.
Toxicologically significant compounds (animals,	Parent compound

plants and environment)	

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral	Males: 11.8 mg/kg bw; Females: 10.5 mg/kg bw
Rat LD_{50} dermal	50 mg/kg bw
Rat LC_{50} inhalation	Males: 63.2 mg/m^3; Females: 76.5 mg/m^3
Skin irritation	Slightly irritant (rabbit)
Eye irritation	Slightly irritant
Skin sensitization (test method used and result)	Not sensitiser (modified Buehler)

Short-term toxicity (Annex IIA, point 5.3)

Target/critical effect	Nervous system / Cholinesterase inhibition
Lowest relevant oral NOAEL/NOEL	NOAEL: 0.03 mg/kg bw (56-d-rat; LOAEL: 0.06 mg/kg bw) according to JMPR criteria.
Lowest relevant dermal NOAEL/NOAL	1 mg/kg bw (21-d-rat; LOAEL: 15 mg/kg bw) according to JMPR criteria.
Lowest relevant inhalation NOAEL/NOEL	1.1 mg/m^3 (90-d-rat)

Genotoxicity (Annex IIA, point 5.4)	Not mutagenic.

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect	Cholinesterase inhibition
Lowest relevant NOAEL/NOEL	*oral, 2 years, rat: 2 ppm (0.1 mg/kg bw/day)*
Carcinogenicity	negative

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target/critical effect	Parental and pups ChE inhibition
Lowest relevant reproductive NOAEL/NOEL	NOEL (rat) 0.1 mg/kg bw
Developmental target/critical effect	None
Lowest relevant developmental NOAEL/NOEL	2.5 mg/kg bw (highest dose treated)

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7)

Delayed neuropathy only at very high doses (3-4 times higher than the LD_{50}, hen).
No potential for delayed neuropathy (rat)

Other toxicological studies (Annex IIA, point 5.8)

NOAEL 0.3 mg/kg bw from 21-d-human study (1:9 ratio methamidophos:acephate; plasma ChE inhibition)

Medical data (Annex IIA, point 5.9)

1.1.1 Some Authors claim that this compound would induce a peripheral neuropathy starting a few days after severe overexposure (so called 'intermediate syndrome'). The clinical, pathological and functional features of these neuropathies have been extensively discussed in the literature, leading to conclude that the existence of this disease as a separate nosological entity is not yet demonstrated.

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI	0.004	21 days human	10
AOEL	0.004	21 days human	10
Drinking water limit			
ARfD (Acute Reference Dose)	0.004	21 days human	10

Dermal absorption (Annex IIIA, point 7.3)

10% (modified estimate from in vivo and in vitro studies)

Acceptable exposure scenarios (including method of calculation)

Operator	Exposure with PPE acceptable only for field crops or in crops with application rate less than 0.7 kg a.i. or for a limited work rate/day
Workers	Re-entry activities should be conducted after 48 hours from last spraying.
Bystanders	A 20 mt. buffer zone is recommended for dwellings.

Chapter 2.4: Residues

Metabolism in plants (Annex IIA, point 6 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Pome fruit [1] Peach[1] [2] incl. nectarine Tomato Pepper, sweet[1] Cucumber Fowering brassica[1] (Cauliflower/Broccoli) Cabbage (red, white, Savoy) Kohlrabi Potatoes Maize / Corn Sugar an fodder beet Tobacco Ornamentals
Rotational crops	No
Plant residue definition for monitoring	Methamidophos
Plant residue definition for risk assessment	Methamidophos
Conversion factor (monitoring to risk assessment)	

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Rat, lactating goat, laying hen,
Animal residue definition for monitoring	Methamidophos
Animal residue definition for risk assessment	Methamidophos
Conversion factor (monitoring risk assessment)	
Metabolism in rat and ruminant similar (Yes/No)	Yes
Fat soluble residue (Yes/No)	Yes

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

Due to the very rapid degradation of methamidophos in soil investigations on the behaviour in succeeding crops are not necessary.

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 introduction)

Data of freezer storage stability studies indicate adequate stability of methamidophos in a variety of crops, in some processed products of these crops, and in commodities of animal origin for intervals ranging from 1 to 26 months. Methamidophos is determined to be stable during frozen storage for up to 26 months in various crops and up to 3 months in most of the animal commodities.

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: [1] yes	Poultry: [1] no	Pig: [1] no
Muscle	0.01*	0.033**	
Liver	0.01*	0.003**	
Kidney	0.01*	0.005**	
Fat	0.01*	0.003**	
Milk	0.01*		
Eggs		0.008**	

*LOD

**Fed with 20 ppm, 200 times higher than estimated intake.

Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2) :

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL	STMR (b)
Broccoli and cauliflower	N	11 x 0.01, 0.04	MRL can be set	0.01 mg/kg	0.01 mg/kg
Cabbage	N	3 x 0.01, 0.015, 0.02, 0.03, 0.05 * , 0.07 *	MRL can be set	0.18 mg/kg	0.018 mg/kg
Cotton	IMPORT	9 x 0.01, 3 x 0.02, 2 x 0.05, 0.12, 0.21			
Cucumber	S	0.12, 0.14, 0.17, 0.23, 0.24, 0.33*, 0.48*	6 more trials are needed for glasshouse, MRL set provisionally	0.5 mg/kg	0.23 mg/kg
Kohlrabi	N	3 x 0.01	One more trial is required	0.01 mg/kg	0.01 mg/kg
Maize	S	11 x 0.01	MRL can be set	0.01 mg/kg	0.01 mg/kg
Peaches and nectarines	S	0.07, 2 x 0.09, 0.1, 0.12, 0.16, 2 x 0.27, 0.29, 0.38, 0.46	MRL can be set	0.5 mg/kg	0.16 mg/kg
Peppers	S	0.06*, 0.14, 3 x 0.17*, 0.18, 0.19, 0.29, 0.37, 0.43, 0.52*, 0.6, 0.78*, 0.95*, 3 x 1.8*	MRL can be set	2 mg/kg	0.43 mg/kg
Pome fruit	S	0.08, 2 x 0.14, 0.24, 0.31, 0.32, 0.4, 0.49	MRL can be set	0.5 mg/kg	0.275 mg/kg
Potatoes	N+S	14 x 0.01, 0.02	MRL can be set	0.01 mg/kg	0.01 mg/kg
Soybean	IMPORT	3 x 0.01, 2 x 0.02, 0.03, 0.09, 0.1			
Sugarbeet	N+S	0.005, 13 x 0.01	MRL can be set	0.01 mg/kg	0.01 mg/kg
Tomato	S	0.15, 0.17, 0.22, 0.27. 0.32, 0.54	Four more triasl are required, MRL set provisionally	0.5 mg/kg	0.245 mg/kg

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x < 0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the critical GAP

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.004 mg/kg bw/day
TMDI (European Diet) (% ADI)	42.48%
NEDI (IEDI) (% ADI)	1.69%
Factors included in NEDI (IEDI)	For the IEDI (WHO European Diet) calculations, the following processing factors (PF) were applied: 0.01 for cottonseed; 0.13 for soybeans; 0.2 for sugarbeets; 4.05 for tomato paste, 1.44 for tomato puree, and 0.93 for tomato juice. The WHO consumption data are not broken down into the individual processed fractions for cabbage, peppers, peaches, and pome fruit. A "weighted processing factor" was applied, using the ratio of raw commodity to the corresponding processed fraction provided in the German consumption survey. These ratios were used to determine the amount consumed as raw cabbage, peppers, peaches, and pome fruit and that consumed as processed. For pome fruit, the ratio of raw to processed fraction is 27:73, for cabbage, 16:84, for peppers, 50:50, and for peaches, 33:67. The processing factor for apple was calculated as follows: Processing factor = (raw fraction x wash factor) + (processed fractions x average PF) = (0.27 x 0.83) + (0.73 x 0.67, which is average of juice and sauce) = 0.71 The same procedure was followed for cabbage, peppers, and peaches, giving the following factors: 0.89 (cabbage); 0.68 (peppers); and 0.54 (peaches).
ARfD	0.004 mg/kg bw/day
Acute expsosure (% ARfD)	NESTI methodology which uses the 97.5 th percentile consumption estimate on a commodity basis, one commodity at a time. The acute RfD (0.004 mg/kg bw/day) is exceeded for peppers and tomatoes for adults, and for apple, pear, peach, nectarine, pepper, tomatoes for toddlers The probabilistic approach indicates that the daily acute intake is well below the aRfD of 0.004 mg/kg bw/day

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/processed crop	Number of studie	Transfer factor	% Transference*
Apple/Washed	3	0.83	
Apple/Sauce	3	0.81	
Apple/Juice	3	0.52	
Apple/Pomace wet	3	0.21	
Cabbage/Cooked	1	0.85	

Crop/processed crop	Number of studie	Transfer factor	% Transference*
Cottonseed /Meal	1	0.58	
Cottonseed /Oil	1	0.01	
Peaches/Washed	2	0.64	
Peaches/Juice	2	0.34	
Peaches/Jam	2	0.62	
Peaches/Preserves	2	0.52	
Peppers/ Dehydration	1	9.00	
Soybeans/Meal	1	1.6	
Soybeans/ Oil	1	0.13	
Tomatoes/ Juice	6	0.93	
Tomatoes/ Puree	3	1.44	
Tomatoes/ Paste	1	4.05	
Tomatoes/ Canned	3	0.79	
Tomatoes/ Cooked	2	0.94	
Sugarbeet/ Sugar	1	0.2	
Potato	not investigated		
Maize	not investigated		
Cucumber	not investigated		
Cauliflower/broccoli	not investigated		
Kohlrabi	not investigated		

* Calculated on the basis of distribution in the different portions, parts, or products as determined through balance studies.

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Group	proposed EU MRL (mg/kg)	established EU MRL (mg/kg)
Pome fruit	0.5	0.05[1)]
Stone fruit Peaches (incl. nectarines) Apricots	0.5	 0.05[1)] 0.1[1)]
Tomatoes	0.5	0.5
Peppers	2.0	0.01*[1)]
Cucumbers	0.5	1.0
Flowering brassica Cauliflower and Broccoli	0.01	0.5[1)]
Head cabbage	0.1	0.5
Kohlrabi	0.01*	0.01*
Cotton seed Soybeans	0.2 0.2	0.1 0.01*
Potatoes	0.01*	0.01*
Cereals Maize	 0.01*	0.01*
Sugar beet	0.01*	not established

Tobacco	25 (green leaves) 25 (dried leaves)	not established
Products of animal origin (incl. milk and eggs)	0.01*	0.01*

Chapter 2.5: Fate and Behaviour in the Environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days	49% after 5 days
Non-extractable residues after 100 days	31% after 5 days
Relevant metabolites - name and/or code, % of applied (range and maximum)	S-methyl phosphoramidate *(M05)* is the major metabolite; desamino-methamidophos *(M01)* is the minor one. Both metabolites in turn degraded rapidly under aerobic conditions to CO_2, the principal degradation product.

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation	Methamidophos degrades rapidly in soil under anaerobic conditions. S-methyl phosphoramidothioate is the major metabolite and seems to not degrade under anaerobic conditions
Soil photolysis	Photodecomposition of methamidophos on a thin layer of sandy loam soil by continuous simulated sunlight is rapid. S-methyl-phosphoramidothioate *(M05)* is the major photoproduct and desamino-methamidophos *(M01)* is the minor one. Soil pH seems to have limited effect on photolysis of methamidophos

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Method of calculation	Where reported the method was 1st order regression
Laboratory studies (range or median, with n value, with r^2 value)	DT_{50lab} (20°C; aerobic) : ranges from 14 h to 6.1 days. Mean values: 3.3 days (n=6). Median: 2.75 days. A degradation DT50 evaluated with 1st order regression on two soils gives 2.1 days with n=4 and r^2=0.895, and 3.4 days with n=4 and r^2=0.954.
	DT_{90lab} (20°C; aerobic) : only one DT90 was evaluated in a degradation study: DT90=6.99 days, r^2=0.895, n=4
	DT_{50lab} (10°C; aerobic) : not provided

	DT_{50lab} (20°C; anaerobic) : 4days
	degradation in the saturated zone : Studies were not performed because methamidophos and its degradates are not expected to leach below the root zone
Field studies (state location, range or median with n value)	DT_{50f}: The half-lives were estimated to be less than 2 days in the trials conducted in Germany (Monheim, Burscheid, Leichlingen) and less than one day in an US, California (Chualar, Fresno) trial
	DT_{90f}: the maximum value has been less than 10 days
Soil accumulation and plateau concentration	Studies not necessary since the DT90 field values for methamidophos are less than 10 days.

Soil adsorption/desorption (Annex IIA, point 7.1.2) :

K_f/K_{oc}	K_{oc}: from 0.88 (clay loam) to 5.69 (high organic silty clay loam).
K_d	K_d: from 0.029 to 0.12
pH dependence (yes/no) (if yes type of dependence)	Adsorption decreases by increasing temperature and decreasing pH.

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching	Little of the compound methamidophos was retained in any soil type. The percentage of originally applied methamidophos leaching through the soil columns ranged from 0 to 20%.
Aged residues leaching	Approximately 80% of the original applied radioactivity was lost during the ageing process of 30 days. Only 5% of the applied aged residues (corresponding to about 1% of radioactivity applied to soil before ageing) was found in the leachate. More than 80% of the applied aged residues was retained in the upper 1.25 cm
Lysimeter/field leaching studies	Not available. Nevertheless in field studies methamidophos residues were not detected below 30.5 cm soil depth at a limit of detection of 0.01 ppm

PEC (soil) (Annex IIIA, point 9.1.3)

Method of calculation

Initial concentrations in soil were calculated based on the assumptions of 50% soil coverage by vegetation, a homogenous distribution in the upper 5 cm of soil and a soil density of 1.5 kg/L. A dissipation half-life of 2 days (field studies) for methamidophos was used.

Application rate

Application rates and initial PECs for the different crops are given below:

Crop	App.rate (kg/ha)	PEC_i(mg/kg)
Field Crops	0.8	0.53
Orchard Crops	1.2 (0.5)	0.8 (0.33)
Ornamentals	1.2 (0.4)	0.8 (0.27)
Vegetables	1.2 (0.5)	0.8 (0.33)

The multiple applications were calculated considering seven application on potatoes spaced 10 days, with an increasing coverage of the soil by potatoes plants.

% coverage	App.rate (kg/ha)	PEC_i(mg/kg)
17	0.6	0.33
43	0.5	0.53
50	0.48	0.16
50	0.72	0.24
50	0.48	0.16
50	0.48	0.16
50	0.72	0.24

PEC(s)		Single application Actual (% of initial)	Single application Time weighted average (% of initial)	Multiple application Actual	Multiple application Time weighted average
Initial		100	100	0.33	0.33
Short-term	24h	70.7	84.5	0.24	0.28
	2d	50	72.1	0.17	0.24
	4d	25	54.1	0.083	0.18
Long-term	7d	8.8	37.6	0.029	0.13
	28d	0.0061	10.3	0.011	0.11
	50d	0	5.8	0.17	0.23
	100d	0	2.9	0	0.022

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (State pH and temperature)	pH 4: DT50 (extrapolated to 22°C) = 1.8 year pH 5: at 25°C, DT50= 309 days
	pH 7: DT50 (extrapolated to 22°C) = 120 hours at 25°C, DT50= 27 days
	pH 9: DT50 (extrapolated to 22°C) = 70 hours at 25°C, DT50= 3 days
Photolytic degradation of active substance and relevant metabolites	Photolysis of methamidophos in aqueous solutions follows first-order kinetics either by continuous simulated sunlight and natural sunlight. The two half-lives differs for a factor 2.4: 37 days for simulated sunlight and 90 days for natural sunlight. Desamino-methamidophos and S-methyl phosphoramidothioate are the major photoproducts
Readily biodegradable (yes/no)	Not performed
Degradation in water sediment - DT_{50} water - DT_{50} water - DT_{50} whole system - DT_{50} whole system	(ditch): 4 days (pond): 7.8 days (ditch, loamy silt): 4.1 days(DT90=13.8 days) (pond, loamy sand): 5.8 days (DT90=19.3 days)
Mineralization	At day 60th: 69.8% (ditch, loamy silt) and 71.9%(pond, loamy sand)
Non-extractable residues	30.3% in ditch and 20% in pond at day 32; 23%in ditch and 15.5% in pond at day 60
Distribution in water/sediment systems (active substance)	The active ingredient was degraded very rapidly in both systems. After an incubation time of 32 days only 0.4% (ditch) and 1.2% (pond) of the applied methamidophos was still detectable in the total systems.
Distribution in water / sediment systems (metabolites)	There was no metabolite ever reaching a level of 10% of the applied radioactivity at any processing date during the experiment. Maximum amounts of individual metabolites were found in the first week of incubation.

PEC (surface water) (Annex IIIA, point 9.2.3)

Method of calculation	Initial concentrations in water resulting from drift input are calculated using the German BBA/UBA drift estimates for various crops at different distances from the treatment site. Estimated initial aquatic concentrations (PEC_i) assumes first-order kinetics for dissipation of methamidophos. A measured half-life for aquatic dissipation of methamidophos of 5.8 days (derived from water/sediment study) was used for these calculations. A water body of 30 cm depth was considered

Application rate

Application rates, % of drift, distance from water body and initial PECsw for the different crops are given below:

Crop	kg/ha	%drift	PEC_{sw}(µg/L)
Field Crops	0.8	4(1m)	10.7
Orchard Crops	1.2 (0.5)	29.6(3m)	118 (49.3)
Orchard Crops	1.2 (0.5)	15.5(3m)	62 (25.8)
Ornamentals	1.2 (0.4)	1.5(10m)	1.8 (0.6)
Vegetables	1.2 (0.5)	12.5(5m)	50 (20.8)

Main routes of entry

Spray drift has been considered the main route of contamination for surface water. Due to the rapid dissipation of the a.i., run-off is not likely to occur

$PEC_{(sw)}$		Single application Actual % of initial	Single application Time weighted average % of initial	Multiple application Actual	Multiple application Time weighted average
Initial		100	100		
Short-term	24h	88.74	94.26		
	2d	78.74	88.95		
	4d	62.00	79.49		
Long-term	7d	43.32	67.75		
	14d	18.77	48.55		
	21d	8.13	36.61		
	28d	3.52	28.83		
	42d	0.66	19.79		

PEC (sediment)

Method of calculation

Not available. In both water/sediment systems the maximum amount of radioactivity in the sediment was reached after 32 days of incubation (ditch: 33%, pond: 24%, of applied). It was reduced by 8 and 6% until termination of the experiment, respectively.

Application rate

$PEC_{(sed)}$	Single application *Actual*	Single application *Time weighted average*	Multiple application *Actual*	Multiple application *Time weighted average*
Initial				
Short-term				
Long-term				

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	Modelling with PELMO For the scenario the weather data from Hamburg (1961) were used and a 10 year period of continuous application of the active ingredient was assumed. As soil scenario a loamy sand was used and a DT50 of 2 days derived from dissipation studies.
Application rate	A multiple applications scenario was considered: seven application on potatoes spaced 10 days, with an increasing coverage of the soil by potatoes plants.

% coverage	App.rate (kg/ha)	PEC_i(mg/kg)
17	0.6	0.33
43	0.5	0.53
50	0.48	0.16
50	0.72	0.24
50	0.48	0.16
50	0.48	0.16
50	0.72	0.24

PEC (gw)

Maximum concentration	0.000 µg/L
Average annual concentration	0.000 µg/L

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air	-
Quantum yield of direct phototransformation	The chemical lifetime of methamidophos in the troposphere was calculated to the procedure described by Atkinson. On account of the molecular structure it can be taken for granted with great certainty that mainly reactions with photochemically produced OH-radicals determine the degradation rate and lifetime of methamidophos in the air. Based on the mean OH-radical concentration a half-life of 0.578 days was calculated and a chemical lifetime in the troposphere of 0.838 days.
Photochemical oxidative degradation in air	Latitude : Season : DT_{50}
Volatilisation	from plant surfaces : 36% in 24 h
	from soil : 1.9%

PEC (air)

Method of calculation	-

PEC (a)

Maximum concentration	-

Definition of the residues (Annex IIA, point 7.3)

Relevant to the environment	Methamidophos was efficiently mineralised to CO_2 under aerobic conditions. Under natural use conditions only very low levels of metabolites will be found in soil, and methamidophos itself can be regarded as the relevant residue.

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	-
Surface water (indicate location and type of study)	-
Ground water (indicate location and type of study)	-
Air (indicate location and type of study)	-

Chapter 2.6: Effects on Non-Target Species

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Acute toxicity to *mammals*	LD_{50} oral rabbit 10 mg/kg b.w.
Acute toxicity to birds	LD_{50} *Junco hyemalis* 8 mg/kg b.w.
Dietary toxicity to birds	5 day LC50 Bobwhite quail 42 mg/kg/diet
Reproductive toxicity to birds	NOEC Bobwhite quail 3 mg/kg/diet

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Application rate (kg as/ha)	Crop	Category *(e.g. insectivorous bird)*	Time-scale	TER	Annex VI Trigger
Birds					
1.2	Orchards, Ornamentals, Vegetables	small insectivorous	acute	**1.74**	10
1.2	Orchards, Ornamentals, Vegetables	large insectivorous	acute	**5**	10
1.2	Orchards, Ornamentals, Vegetables	Insectivorous	short-term	**2.18** **3.4°**	10
1.2	Orchards, Ornamentals, Vegetables	Insectivorous	long-term	**0.16** **3.64°**	5
1.2	Orchards, Ornamentals, Vegetables	small granivorous	acute	**0.97**	10
1.2	Orchards, Ornamentals, Vegetables	large granivorous	acute	**2.9**	10
1.2	Orchards, Ornamentals, Vegetables	granivorous	short-term	**1.31** **1.88°**	10
1.2	Orchards, Ornamentals, Vegetables	granivorous	long-term	**0.09** **1.99°**	5
1.2	Orchards, Ornamentals, Vegetables	small eating leaves	acute	**0.9**	10
1.2	Orchards, Ornamentals, Vegetables	large eating leaves	acute	**2.7**	10
1.2	Orchards, Ornamentals, Vegetables	eating leaves	short-term	**1.12** **1.76°**	10
1.2	Orchards, Ornamentals, Vegetables	eating leaves	long-term	**0.08** **1.86°**	5
1.2	Orchards, Ornamentals, Vegetables	small erbivourus	acute	**0.25**	10

1.2	Orchards, Ornamentals, Vegetables	large erbivourus	acute	0.75	10
1.2	Orchards, Ornamentals, Vegetables	erbivourus	short-term	0.31 0.5°	10
1.2	Orchards, Ornamentals, Vegetables	erbivourus	long-term	0.02 0.52°	5
1.2	Orchards, Ornamentals, Vegetables	small frugivorous	acute	21.49	10
1.2	Orchards, Ornamentals, Vegetables	large frugivorous	acute	67	10
1.2	Orchards, Ornamentals, Vegetables	frugivorous	short-term	27 42°	10
1.2	Orchards, Ornamentals,vegetables	frugivorous	long-term	2 44°	5

° Short and long term toxicity exposure ratios TWA PEC (half-life 3.6; short term: 64.21% of initial residue after 5; long term 4.33% of initial after 120 day)

Mammals					
1.2	Orchards, Ornamentals,vegetables	small insectivorous mammals	acute	1.73	10
1.2	Orchards, Ornamentals, Vegebles	large mammals insectivorous	acute	5.26	10
1.2	Orchards, Ornamentals, Vegetables	insectivorous Mammals	short-term	0.03 0.3°	10
1.2	Orchards, ornamentals, Vegetables	insectivorous Mammals	long-term	0.53 12.14°	5
1.2	Orchards, ornamentals, Vegetables	small granivorous mammals	acute	0.96	10
1.2	Orchards, ornamentals, Vegetables	large granivorous mammals	acute	2.87	10
1.2	Orchards, ornamentals, Vegetables	granivorous Mammals	short-term	0.01 0.17°	10
1.2	Orchards, ornamentals, Vegetables	granivorous Mammals	long-term	0.29 6.64°	5
1.2	Orchards, ornamentals, Vegetables	Small mammals eating leaves	acute	0.89	10
1.2	Orchards, ornamentals, Vegetables	large mammals eating leaves	acute	2.66	10
1.2	Orchards, ornamentals, Vegetables	Mammals eating leaves	short-term	0.01 0.16°	10

1.2	**Orchards, ornamentals, Vegetables**	Mammals eating leaves	long-term	**0.27 6.21°**	5
1.2	**Orchards, ornamentals, Vegetables**	small erbivourus mammals	acute	**0.25**	10
1.2	Orchards, ornamentals, Vegetables	large erbivourus mammals	acute	**0.74**	10
1.2	Orchards, ornamentals, Vegetables	Erbivourus mammals	short-term	**0.004 0.04°**	10
1.2	Orchards, ornamentals, Vegetables	Erbivourus mammals	long-term	**0.07 1.72°**	5
1.2	Orchards, ornamentals, Vegetables	small mammals eating fruit	acute	21.4	10
1.2	Orchards, ornamentals, Vegetables	large mammals eating fruit	acute	64.1	10
1.2	Orchards, ornamentals, Vegetables	Mammals eating fruit	short-term	**0.32 3.7°**	10
1.2	Orchards, ornamentals, Vegetables	Mammals eating fruit	long-term	6.41 148°	5

° Short and long term toxicity exposure ratios TWA PEC (half-life 3.6; short term: 8.66% of initial residue after 56; long term 4.33% of initial after 120 day)

Toxicity data for aquatic species (most sensitive species of each group)

(Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/l)
Laboratory tests				
1.1.1.1 Oncorhynchus mykiss	Methamidophos techn	96h	LC50	40
1.1.1.2 Oncorhynchus mykiss	Methamidophos techn	97 d	NOEC	2.15
1.1.1.3 Daphnia magna	Methamidophos techn	48h	EC50	0.27
1.1.1.4 Daphnia magna	Methamidophos techn	21d	NOEC	0.026
1.1.1.5 Scenedesmus subspicatus	Methamidophos techn	96h	EC_{50} (growth inhibition)	> 178
Oncorhynchus mykiss	600 EC	96h	LC_{50}	112
Scenedesmus subspicatus	600 SL	96h	EC_{50} (growth inhibition)	202
Microcosm or mesocosm tests: No data available				

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

Application rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
0.8	Field Crops	*Oncorhynchus mykiss*	96 h	1	3738	100
1.2	Orchard Crops Early growth stage	*Oncorhynchus mykiss*	96 h	3	339	100
1.2	Orchard Crops Late growth stage	*Oncorhynchus mykiss*	96 h	3	645	100
1.2	Ornamentals	*Oncorhynchus mykiss*	96 h	10	22222	100
1.2	Vegetables	*Oncorhynchus mykiss*	96 h	5	800	100
0.8	Field Crops	*Daphnia magna*	48 h	1	25	100
1.2	Orchard Crops Early growth stage	*Daphnia magna*	48 h	3	2	100
1.2	Orchard Crops Late growth stage	*Daphnia magna*	48 h	3	4	100
1.2	Ornamentals	*Daphnia magna*	48 h	10	150	100
1.2	Vegetables	*Daphnia magna*	48 h	5	5	100
0.8	Field Crops	*Scenedesmus subspicatus*	96 h	1	16636	10
1.2	Orchard Crops Early growth stage	*Scenedesmus subspicatus*	96 h	3	1508	10
1.2	Orchard Crops Late growth stage	*Scenedesmus subspicatus*	96 h	3	2871	10
1.2	Ornamentals	*Scenedesmus subspicatus*	96 h	10	98889	10
1.2	Vegetables	*Scenedesmus subspicatus*	96 h	5	3560	10
0.8	Field Crops	*Oncorhynchus mykiss*	97 d	1	201	10
1.2	Orchard Crops Early growth stage	*Oncorhynchus mykiss*	97 d	3	18	10
1.2	Orchard Crops Late growth stage	*Oncorhynchus mykiss*	97 d	3	35	10
1.2	Ornamentals	*Oncorhynchus mykiss*	97 d	10	1194	10
1.2	Vegetables	*Oncorhynchus mykiss*	97 d	5	43	10
0.8	Field Crops	*Daphnia magna*	21 d	1	2.43	10
1.2	Orchard Crops Early growth stage	*Daphnia magna*	21 d	3	0.22	10
1.2	Orchard Crops Late growth stage	*Daphnia magna*	21 d	3	0.42	10
1.2	Ornamentals	*Daphnia magna*	21 d	10	14.44	10
1.2	Vegetables	*Daphnia magna*	21 d	5	0.52	10
0.8	Field Crops	*Daphnia magna*	21 d	1	6.64*	10
1.2	Orchard Crops Early growth stage	*Daphnia magna*	21 d	3	0.60*	10
1.2	Orchard Crops Late growth stage	*Daphnia magna*	21 d	3	1.15*	10
1.2	Ornamentals	*Daphnia magna*	21 d	10	39.47*	10

1.2	Vegetables	*Daphnia magna*	21 d	5	**1.42***	10

* Refinement of risk with TWA PEC_{sw} (36.61% of initial residue half-life 5.8)

Bioconcentration

Bioconcentration factor (BCF)	Methamidophos lacks a potential for bio-accumulation, as indicated by a log P_{ow} of -0.8
Annex VI Trigger for the bioconcentration factor	100
Clearance time (CT_{50})	
(CT_{90})	
Level of residues (%) in organisms after the 14 days depuration phase	

Effects on honeybees (Annex IIIA, point 10.4)

Acute oral toxicity (72 hrs)	No data have been provided
Acute contact toxicity (72 hrs)	No data have been provided

Hazard quotients for honey bees (Annex IIIA, point10.4)

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
				50
				50
				50
Field or semi-field tests				
				50
				50

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Species	Stage	Test substance	Dose (kg as/ha)	Endpoint	Effect	Annex VI Trigger
Laboratory tests						
Amblyseius potentillae (S)	adult	Tamaron SL 600	0.108	Mortality	100%	30%
Amblyseius potentillae (R)	adult	Tamaron SL 600	0.108	Mortality	100%	30%
Typhlodromus pyri (S)	adult	Tamaron SL 600	0.108	Mortality	100%	30%
Typhlodromus pyri (R)	adult	Tamaron SL 600	0.108	Mortality	100%	30%
Chrysoperla carnea	larvae	Tamaron SL 600	0.18	Mortality	100%	30%
Field or semi-field tests						
No data available						

S = susceptible R = resistant

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity	LC50: 28.8 form/kg d.w. soil *Eisenia foetida* LC50: 73 form/kg d.w. soil *Eisenia foetida* NOEC: 1 mg form/kg d.w. soil *Eisenia foetida*
Reproductive toxicity	no data

Toxicity/exposure ratios for earthworms (Annex IIIA, pont 10.6)

Application rate (kg as/ha)	Crop	Time-scale	TER	Annex VI Trigger
0.8	Field Crops	acute	138	10
1.2	Orchards, Ornamentals Vegetables	acute	91	10
0.8	Field Crops	acute	54	10
1.2	Orchards, Ornamentals Vegetables	acute	36	10

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralization	no meaningful influence on the mineralization of nitrogen.
Carbon mineralization	no meaningful influence on the mineralization of carbon

LEVEL 3

Proposed decision with respect to application for inclusion of the active substance in Annex I

Methamidophos

3. Proposed decision with respect to the application for inclusion of the active substance in Annex I

3.1 Background to the proposed decision

Methamidophos is the ISO common name for thiophosphoramidic acid, O,S-dimethyl ester (IUPAC). Methamidophos is an organophosphate insecticide acting by ingestion and contact, formulated as a soluble concentrate. It is used on various crops throughout EU.

An ADI of 0.004 mg/kg b.w. can be set.
An AOEL of 0.004 mg/kg b.w. can also be set.
An ARfD 0.004 mg/kg b.w can also be set.

Based on the data submitted, the use of plant protection products containing methamidophos in accordance with the proposed GAPs exceeds in certain instances the AOEL unless certain restrictions to the use are applied and adequate PPE is worn.
The daily time of re-entry activities in high crops has to be reduced to a maximum of 2 hours/day, including this limit in the GAP; in alternative, a period of inhibition for access to the area which allows enough time for the residues to decay to a safe level should be proposed.
'Residential bystanders' may be exposed to unacceptable levels of methamidophos if no adequate buffer zone is adopted.
Harmful effects on human health from residues which occur in plants, animal tissue, soil or water as a consequence of use of methamidophos in accordance with the principles of good agricultural practice are not expected. Further residue data are necessary to cover all the intended uses.
As methamidophos is not persistent, prolonged environmental exposure does not have to be expected.
Methamidophos shows a high potential risk for terrestrial vertebrates, although under practical conditions, the risk to birds appears to be low. To identify safe uses a refined risk assessment for both bird and mammals is required. Methamidophos is not hazardous to aquatic organisms, except for aquatic invertebrates. It does not accumulate in fish.
No Hazard Quotients for honeybees have been calculated, because only higher tier studies have been provided. From a cage field toxicity trial, toxicity to honey bees proved to be very high, but decreased rapidly few days after treatment.
Due to its rapid degradation, Methamidophos does not show a negative impact on earthworms. The risk for beneficial arthropods is high, even if they appear to be able to re-colonise treated fields shortly after the residues fall below the respective toxic thresholds. However, as data provided are insufficient, further studies on beneficial arthropods are necessary. The risk for soil micro-organisms can be considered as negligible.

3.2 Proposed decision concerning inclusion in annex I

A conditional inclusion of the active substance Methamidophos in Annex I of the Directive 91/414/EEC for a period of five years is proposed.

The proposal to set a time-limit on the inclusion is due to fact that further information is needed for a final evaluation.

Restrictions:

Adequate PPE should be worn during mixing/loading and application; in high crops tractor mounted scenario, for which the AOEL saturation is at a higher level, the application rate should be reduced to 1.1-1.0 kg a.i./day; re-entry activities into the treated field should not exceed two hours/day after the application.

A buffer zone of 20 meters to protect 'residential bystanders' is required.

Buffer zones to protect aquatic invertebrates are required.

Methamidophos should not be used during the flowering to protect honeybees.

3.1 Rationale for the proposed decision

The data provided indicate no concern for human or animal health from uses of Methamidophos if the recommended restrictions are adopted. A complete assessment on the toxicity to beneficial artropods can only be done when required supplementary information is provided.

The acute RfD is exceeded for some crops if calculated according to the NESTI approach. This approach is considered to be extremely conservative, and the more realistic probabilistic approach indicated a daily acute intake well below the RfD. It is therefore expected that methamidophos does not pose any acute dietary risk for humans.

For a proper definition of MRL, for all intended uses, further data are necessary.

LEVEL 4

Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex I

Methamidophos

4.2 Physical and chemical properties

Annex IIA, 2.7:

Solubility in organic solvents.

Justification:

The study submitted is not acceptable because it is done on purified active substance and not on active substance as manufactured.

4.3 Residue data:

Annex IIA 6.3 and Annex IIIA 8.1

Residues resulting from supervised trials

Cucumber: 6 more trials are needed for glasshouse

Kohlrabi: One more trial is required

Tomato: Four more triasl are required

Justification:

The minimum requirements are not fullfilled for these crops.

Annex IIA 6.6 and Annex IIIA 8.2

Effects of industrial processing and/or household preparation on the nature and magnitude of residues.

Processing studies are needed for: potato, maize, cucumber, cauliflower/broccoli and kohlrabi.

Justification:

No information is provided.

4.4 Environmental fate and behaviour:

Annex IIIA 9.2.1

Application of the PELMO model to all scenarios that were proposed within the FOCUS group

Justification:

An identification of possible leaching scenarios of methamidohos.

4.5 Ecotoxicology:

Annex IIA 8.1 and Annex III 10.1

Refined risk assessment for both bird and mammals, to identify safe uses, is required.

Justification:

Risk for birds and mammals is very high.

Annex IIA 8.3 and Annex III 10.4

Higher tier studies on non-target arthropods *Aphidius rhopalosiphi* and *Typhlodromus pyri* (with a dose/response approach) are required.

Justification:

Data provided are insufficient.

Opinion of the Scientific Panel on Plant health, Plant protection Products and their Residues on a request from the Commission related to the evaluation of methamidophos in toxicology in the context of Council Directive 91/414/EEC[1].

(Question N° EFSA-Q-2004-60)

Adopted on 14 September 2004

SUMMARY OF OPINION

The PPR Panel was requested by EFSA to address the following question, *"The provided dermal absorption data on methamidophos are apparently conflicting. What value for the degree of dermal absorption would be scientifically justified, based on the available data, to use in the assessment of human risk arising from the dermal route of exposure?"*

The PPR Panel concludes that there are several problematic points in the provided dermal absorption studies which, confound the interpretation of the data and do not allow an accurate estimation of methamidophos dermal absorption. The conflicting results obtained are likely due, at least in part, to the formation of volatile metabolites following exposure to methamidophos.

Results from the studies on dermal absorption in monkeys and humans *in vivo*, could serve as a basis for estimating the extent of dermal absorption in humans. This will give a best estimated dermal absorption of the diluted preparation of about 5%. The underlying assumption is that the disposition of methamidophos in the monkey is similar to that in humans. The value of about 5% is consistent with the 10 % value estimated from the monkey study and the fact that data with a number of compounds indicate a 2-3 fold higher skin absorption in monkeys than in humans.
Absorption of the undiluted formulation is lower.

Key words : methamidophos; insecticide; organophosphorus; hydrophilic; mercaptan; dermal absorption, human.

[1] For citation purposes: Opinion of the Scientific Panel on Plant Health, Plant Protection Products and their Residues on a request from the Commission related to the evaluation of methamidophos in toxicology in the context of Council Directive 91/414/EEC, *The EFSA Journal* (2004),95, 1-15.

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BACKGROUND

Methamidophos is used as an insecticidal compound and is included in the first list of active substances referred to in Article 8(2) of Directive 91/414/EEC[2] concerning the placing of plant protection products on the market. On the basis of the evaluation report prepared by Italy as Rapporteur Member State (RMS), the substance has been peer reviewed with Member State experts in the working group "Plant Protection Products – Evaluation". A tripartite meeting with the RMS and the main data supplier was also organised.
The Peer Review identified several data gaps, which were addressed by the notifier. All information submitted has been evaluated and discussed with Member States in the Working groups "Evaluation".
An outstanding issue was identified which needs to be resolved in the risk assessment of the operators' exposure (Dermal absorption).
According to a series of studies submitted by the notifier, the dermal absorption was estimated to be 4.84%. This value was derived from the human volunteer study with consideration of the data derived from the Rhesus monkey study (absorption ratio between intravenous and dermal administration).
For the same study, a more conservative approach was proposed with no consideration of the correction factor from the monkey study but with the assumption that the non-recovered amount is potentially absorbed; a significantly higher dermal absorption of 28% is estimated.

TERMS OF REFERENCE

The provided dermal absorption data on methamidophos are apparently conflicting. What value for the degree of dermal absorption would be scientifically justified based on the available data, to use in the assessment of human risk arising from the dermal route of exposure?

ASSESSMENT

1.1. INTRODUCTION

For the evaluation of the degree of dermal absorption of methamidophos and its 600 SL formulation, through human skin, three *in vivo* studies (rat, monkey and human) and one comparative *in vitro* study (rat–human) on dermal absorption were provided to the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR) and have been evaluated. In addition, three repeated exposure studies (two *via* the oral and one *via* the dermal route) were evaluated by the PPR Panel for comparison of the oral and dermal doses producing the same degree of cholinesterase (ChE) inhibition in plasma and red blood cells (RBC). This comparison was considered to provide useful supplementary information in the light of the limitations observed in the dermal absorption studies.

[2] OJ No L 230, 19.08.1991, p.1.

Methamidophos, (O,S-dimethyl phosphoramidothiate) is a water-soluble organophosphorus compound, with log Pow = -0.80 at 20° C and MW= 141.1. The chemical structure is as shown in Figure 1.

The acute oral LD_{50} of methamidophos in the rat ranges between 13 and 32 mg/kg b.w., depending on the vehicle, sex and dosing conditions while the acute dermal LD_{50} for rat is in the range of 108 -162 mg/kg b.w.

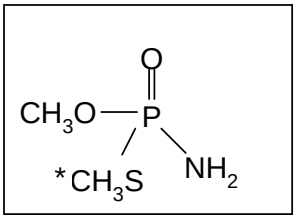

Figure 1. Chemical structure of methamidophos and location of the radioactive label (*)

The main confounder identified in all four evaluated dermal absorption studies is the position of the radioactive label in the methamidophos molecule (Figure 1). When S-Methyl-^{14}C-methamidophos is administered, volatile metabolites are formed, the main one of which is the unstable compound methylmercaptan (CH_3SH). This would not be effectively retained in the trap systems used (when used), which would lead to relatively low recovery of the applied radioactivity and to increased uncertainty in the results obtained. Additional loss of the radioactivity could have occurred due to hydrolysis of methamidophos on the skin surface prior to absorption.

1.2. AVAILABLE DATA ON DERMAL ABSORPTION

1.2.1. *IN VITRO* STUDY

S-Methyl-^{14}C-methamidophos was studied for *in vitro* penetration through viable human and rat skin membranes. Methamidophos was tested as technical substance at the following concentrations of technical active ingredient (a.i.): 1.93 g/l, 60 g/l or 601 g/l, corresponding to 0.03, 0.94 or 9.4 mg.cm^{-2}, for a 24-hour period of exposure. The formulated product (Tamaron 600 SL) was also tested as formulation (approx. 48 %) and as a 333-fold aqueous dilution (approx 1g/l), which correspond to approximately 7.7 and 0.016 mg.cm^{-2}, respectively. Samples of 200 µl were taken from the receptor fluid at 1, 2, 4, 6, 8, 10, 20, 22 and 24 hr. The recovery of radioactivity was close to 100% in most cases. Following methamidophos technical application, for the low, middle and high dose, respectively, 36.3% 11.6% and 3.3% of the

applied radioactivity was associated with human skin membrane after washing. With the rat skin membrane, the values were 50.6%, 27.6% and 4.7%, respectively. The respective amounts of radioactivity detected in human skin membranes following exposure to the formulation and to the 333-fold aqueous dilution were 1.8% and 23.0% of the applied radioactivity, and 20.0% and 54.4% in the rat skin membranes.

The relative *in vitro* penetration through human skin membrane for methamidophos technical after 24 hr. of exposure was 1.05%, 0.81% and 0.29% of the applied radioactivity (low, middle, high dose) and through rat skin it was 2.4%, 9.77% and 1.24%[3], (low, middle, high dose). The flux values were 0.01, 0.38, 11.9 $\mu g.cm^{-2}.h^{-1}$ for human skin and 0.033, 4.33, 4.38[3] $\mu g.cm^{-2}.h^{-1}$ for rat skin, at the respective dose levels. It should be noted that methamidophos caused pycnosis of rat skin membranes at the highest concentration of the technical active ingredient.

The relative penetration through human skin for methamidophos formulation after 24 hr. of exposure was 0.18% and 0.71% for the formulation and aqueous dilution (333-fold aqueous dilution, maximum field concentration), respectively. The respective values for rat skin were 29.8% and 7.54%[3]. The flux values for the concentrate and the dilution were 1.11 and 0.01$\mu g.cm^{-2}.h^{-1}$ for human skin membrane and 140 and 0.07[3] $\mu g.cm^{-2}.h^{-1}$ for rat skin, respectively. Pycnosis of the rat skin membranes was evident with the aqueous dilution of the 600 SL formulation. In addition, rat skin membranes treated with this preparation showed greater leakage than the corresponding control membranes.

In conclusion, data from rat skin membranes exposed to the highest concentration of the technical a.i. and to the aqueous dilution of the 600 SL formulation were unreliable and are not considered further here. The highest relative *in vitro* penetration of methamidophos technical through human skin at 24 hr. of exposure was 1.05% at the lowest concentration tested. Based on the relative absorption values of methamidophos technical, rat skin membranes are 2.28 and 12.06 times more permeable than human skin for the low and middle concentration respectively. Based on the flux values, rat skin is 3.3 and 11.4 times more permeable than human skin. The relative *in vitro* penetration through human skin over 24 hours continuous exposure was less than 1% of the applied dose both for the formulation and the aqueous dilution. Based on the relative absorption values, rat skin membranes are 165 times more permeable than human for the concentrated 600 SL formulation. Based on the flux values, rat skin is 126 times more permeable than human skin for the concentrate. The amounts of radioactivity associated with the skin membranes have not been taken into account. (van de Sandt, 1998).

[3] Epidermal pycnosis was observed in rat skin membranes at the highest concentration of methamidophos technical and at the aqueous dilution of the formulation SL 600.
In the skin membrane leakage test with lactate deshydrogenase (LDH), a difference was observed between the rat skin membranes exposed to the aqueous dilution of SL600 and the control group (testosterone).

1.2.2. *IN VIVO* RAT STUDY

S-Methyl-^{14}C-methamidophos (radiochemical purity >99.88%, specific radioactivity of 25.7 mCi/mM) was dissolved in deionised water and applied dermally to 12 male Sprague–Dawley rats per dose group (single application) for an exposure period of 2, 10 or 24 hours at three dose levels, *i.e.* 0.05 mg/rat (1 g a.i./l), 0.5 mg/rat (9.8 g a.i./l), 5 mg/rat (97.2 g a.i./l), on a 10 cm^2 skin area (shaved dorsal trunk, 0.005, 0.05 and 0.5 $mg.cm^{-2}$). Following the scheduled exposure period (2, 10 or 24 hr.), 4 rats from each dose group were killed and the skin from the application site, blood, CO_2 trap, volatiles trap, carcass and excreta were measured for radioactivity.

The mean total recovery of the radioactivity applied was 72.7% (±13%) at 0.05 mg/rat, 75.5% (±8.3%) at 0.5 mg/rat and 80.6% (±6.6%) at 5mg/rat dose group. Most of the absorbed material was recovered in urine and carcass. The systemically absorbed amounts (blood + urine + faeces + methanol cage wash + CO_2 trap + volatiles trap) accounted for 3.9, 6.0 and 5.5%, in the low dose group, 4.7, 9.1 and 10.0% in the middle dose group and 8.0, 19.7 and 16.9% in the high dose group at 2, 10 and 24 hr. of exposure, respectively. Most of the radioactivity that was not systemically absorbed at 24 hr. was found on the skin surface and distributed between the soap/water scrubs and acetone skin rinses. The greatest total recovery of radioactivity, as a function of the duration of exposure, was observed at 2 hr. for all dose groups and decreased at 10 and 24 hr. This observation is explained in the study report with information provided by another ADME (absorption, distribution, metabolism and excretion) study (Crossley and Tutass, 1969, DAR, Vol. 3, Annex B6) where methamidophos was found to be metabolised in the rat mainly via loss of the S-methyl group, thus producing volatile metabolites (mercaptans). In the present dermal absorption study it is suggested that the charcoal trap used did not effectively retain the volatile metabolites formed.

The PPR Panel notes that if the unrecovered amount is considered to be proportionally absorbed (correction back to 100%), the dermal absorption was estimated to be 4.4 % at 2 hr., 9.4 % at 10 hr. and 8.4% at 24 hr. of exposure for the low dose, for the middle dose 5.5% at 2 hr., 12.4% at 10 hr. and 15.2% at 24 hr. of exposure and for the high dose 9.1% at 2 hr., 24.2% at 10 hr. and 23.2% at 24 hr. of exposure.

The approach presented in the DAR was that the unrecovered percentage of the applied dose, (presumably untrapped volatile metabolites), was added to the percent recovered systemically and the total was used as a conservative estimate of dermal absorption {assumed dermal

absorption = % of systemic absorption (blood, urine, faeces, carcass, cage wash, $^{14}CO_2$ trap, volatiles trap) + % not recovered (100% - total measured recovery)}. The dermal absorption was estimated to be 15.2% at 2 hr., 42.4% at 10 hr. and 39.8% at 24 hr. of exposure for the low dose, for the middle dose 18.8% at 2 hr., 35.6% at 10 hr. and 43% at 24 hr. of exposure and for the high dose 20.3% at 2 hr., 38.4% at 10 hr. and 44.1% at 24 hr. of exposure. For reasons presented under point 1.2.4. Human Volunteer Study, most of the unrecovered radioactivity was due to volatile metabolites and the above-presented approach is considered to be a major overestimation.

The data available indicate that methamidophos is absorbed through rat skin *in vivo* in a time dependent manner up to 10 hours of exposure. The dermal absorption of methamidophos in the rat *in vivo* is estimated to be 8-24% for exposure time between 10 and 24-hours for dermal doses of 0.05 - 5mg/rat (Bagos *et al*., 1991).

1.2.3. RHESUS MONKEY STUDY

S-Methyl-^{14}C-methamidophos technical was administered intravenously (*i.v.*) to four male Rhesus monkeys at a single dose of 239±2 µg and 27.7± 0.3 µCi in 1 ml of 0.9% saline. Urine and faeces were collected and blood samples were taken at scheduled time points up to 120 hr. post dosing since radioactivity in urine had declined at 96-120 hr. to only twice the background values.

On Day 15 after the *i.v.* administration of 0.1 ml of methamidophos formulation (600 SL), a similar dose, (mean dose per monkey 239±2 µg and 27.7± 0.2 µCi) was applied dermally on a skin surface area of 4x6 cm^2 (10 µg/cm^2) under non-occlusive protection for 8 hr. Following an exposure period of 8 hr., the application site was washed 16 times with soap and 2 times with isopropyl alcohol (IPA) swabs. The washing was repeated at 24 and 48 hr. with IPA and approximately ¼ of the exposed skin surface area was tape stripped 16 times for the determination of the residual radioactivity associated with the surface layer of the skin. A different area of the dose site was stripped each day. Urine, faeces and feed biscuits were collected and blood samples were taken at scheduled time points up to 120 hr. post dosing. Collection of the excreta was terminated on day 23.

For the *i.v.* dose, a mean of 11.35% of the administered radioactivity was recovered in urine with most being excreted during the first 4 h. Faecal radioactivity represented a mean of 0.51%. The mean recovery (urine, faeces, feed biscuits, *i.v.* catheters) was 11.94%.

For the dermal dose, a mean of 1.18% of the administered radioactivity was recovered in urine. The largest amount was excreted between 12 and 24 hr. post dosing. Faecal radioactivity

represented a mean of 0.06% of the dose applied. Total radioactivity in urine, faeces and contaminated feed was 1.35%. A large percentage of the applied radioactivity was recovered from the application site (57.3 % from the skin soapy swabs; 4.10% from IPA swabs and 0.15% from tape strips). The plasma and RBC radioactivity were near the LOD. The mean total recovery of the administered radioactivity was 66.9%.

In conclusion, the mean dermal absorption of methamidophos in Rhesus monkeys, when calculated on the basis of the amounts of radioactivity excreted in urine, following dermal application, in comparison to the amounts excreted following *i.v.* administration of the same dose, was estimated to be {(1.18/11.35) x100} = 10.4% (Fuller, 2000).

1.2.4. HUMAN VOLUNTEER STUDY

For the investigation of dermal absorption and excretion of S-methyl-^{14}C methamidophos from a 600 SL formulation in healthy male volunteers, 100 µl, containing 71 µg a.i. and 13.7 µCi were applied on an intact skin area of 4x6 cm^2 (3 µg/cm^2 skin area) on the volar region of the forearm. The tested concentration is in the range of the expected field spray concentration of metamidophos 600 SL formulation (approx. 1 mg/L). Six male healthy human volunteers were exposed to the test compound, under non-occlusive protection, for a period of 8 hr. After the removal of the protective enclosures, the skin sites were wiped with a series of sixteen cotton swabs dipped in soapy water, rinsed with a steady stream of soapy water and then swabbed with cottons (2x) dipped in isopropyl alcohol (IPA). For the determination of the amount of residual radioactivity associated with the surface layer of the skin, one sixth of each dosed site was stripped with tape and washed with IPA, approximately 18 and 48 hours after the removal of the test material. A different area of the dosed site was stripped each day. The skin was also swabbed with cotton/IPA on days 5 to 7.

All urine and faeces samples were collected for five days following administration. Venous blood samples were collected from the ipsilateral and contralateral veins during and after the exposure period. The blood samples were centrifuged to separate cells from plasma and plasma samples were analysed for total radioactivity. Additional blood samples were taken for cholinesterase (ChE) measurements.

Protective enclosures, swabs, rinses, gauze, tape strips, urine and faeces were analysed for total radioactivity.

The detected radioactivity in the venous plasma, both for ipsilateral and contralateral samples, was less than twice the background in several samples analysed. Concentrations of radioactivity in plasma increased with time indicating that at 8 hr. the radioactivity had not been completely removed from the site.

A mean of 0.55% of the administered radioactivity was recovered in urine. There was no significant excretion of label in faeces. A mean of 60.7% of the radioactivity could be removed with swabs. The majority of radioactivity detected on the exposed surface of the skin was found mainly in the swabs, skin rinses, protective enclosure and gauze, with a mean of 70.5% of the applied radioactivity. Tape stripping and swabbing of one sixth of the dosed area, removed a mean of 0.58% and 0.40% of applied radioactivity on days 2 and 3 respectively. Since only a sixth of the area was stripped and swabbed, the estimated total amount of radioactivity that could be removed from the skin surface on days 2 and 3 are 3.47 (3.14% tape strips + 0.33% IPA swabs) and 2.40% (2.18% tape strips + 0.22% IPA swabs) respectively. This indicates that a significant amount of radioactivity remained in the epidermal skin layer and could not be removed with soapy water swabs. The mean total recovery of radioactivity was 72.0%. This is similar to the respective values from rat and monkey studies, 67.3% in the latter case.

The mass balance in this study was low. This is most likely explained by the position of the radiolabel and the formation of methylmercaptan as the primary metabolite. Approximately 40% of the administered radioactivity was converted into volatile metabolites in a metabolism study in rat following oral administration of ^{14}C-methamidophos (Crossley *et al.*, 1969, DAR, Vol. 3, Annex B6). Furthermore, in the case of dermal administration, additional loss of radioactivity could have occurred due to degradation and metabolism of methamidophos on the skin surface by esterases to produce methylmercaptan. Methylmercaptan can be lost through volatilization or it can bind to endogenous macromolecules such as sulfhydryl-containing proteins.

Although methamidophos is water-soluble, very thorough swabbing of the skin surface with soapy water after 8 hr. of exposure was not sufficient to remove all of the remaining surface radioactivity. The alcohol washing after 8 hr. of exposure (16 soapy swabs followed by two dry swabs and IPA swabs removed 2.3% of the applied radioactivity and tape stripping/alcohol swabbing on day 2 and 3 removed 3.5 and 2.4%) clearly shows persistence of radioactivity that could not be attributed to a compound with the characteristics of methamidophos itself. Obviously, the detected amounts of radioactivity are characteristic of the metabolites and/or degradation products formed and not of the parent compound. The rat, monkey and human data also are all consistent with the hypothesis that methamidophos is metabolised or degraded to methylmercaptan on the skin surface and that this is either lost by volatilisation or bound to proteins of the skin.

For the human study, a mean of 0.55% of the dermally administered radioactivity was excreted in the urine. This is lower than the respective value from the monkey study (1.2%) and is consistent with previous data on the relative dermal absorption in the two species (ECETOC, 1993). Assuming that urinary excretion in humans after *i.v.* injection would be the same as measured in monkeys (i.e. there are no relevant differences in metabolism between the two species (Miyamoto *et al.*, 1988; Smith *et al.*, 1977), then dermal absorption for human volunteers receiving a single dermal dose of 3 μg.cm^{-2} of S-methyl-^{14}C methamidophos from a 600 SL formulation can be estimated to be 4.8% =0.55 (% urinary recovery of the dermal dose in humans)/11.35 (% urinary recovery of the *i.v.* dose in monkeys) x 100%.

For the reasons explained above, estimation of the dermal absorption of methamidophos through human skin from the systemically determined amount + the unrecovered amount, which corresponds to 28.6% {0.55% + [100 – 72]%} is a major overestimation. This is because the assumption that all unrecovered radioactivity was, in fact, absorbed is unsubstantiated and not plausible (Selim, 2000).

1.3. REPEATED EXPOSURE STUDIES

For comparison purposes between the dose levels of methamidophos that can affect cholinesterase activity after oral and dermal exposure, two repeated dose feeding studies and one dermal exposure study were evaluated. Although these studies were not designed for this purpose the comparison of iso-effective oral and dermal doses, with respect to ChE inhibition, a quantitative biomarker of exposure to OP's, can give some reassurance on the estimation of the dermal absorption factor.

1.3.1. RAT FEEDING STUDIES

Four groups of 15 Wistar rats/sex were administered methamidophos of technical grade (premix 50%) in the diet for three months at concentrations of 2, 6, 20 and 60 ppm (equivalent to 0.15, 0.46, 1.52 and 4.57 mg/kg b.w. for males and 0.19, 0.56, 1.86 and 5.58 mg/kg b.w. for females). In addition, another group of 30 male and 30 female rats were used as controls.

ChE activity measurements were performed on day 8 and at weeks 4, 8 and 13 after the start of the experiment in 5 male and 5 female rats from each group.

A dose dependent decrease of ChE activity was observed in both male and female rats. The NOEL for both plasma and RBC ChE was 2 ppm, based on significantly reduced activity observed

at 6 ppm (52 and 66% of controls for plasma and RBC ChE in males and 76 and 81% for plasma and RBC ChE in females). The lowest ChE activity was observed at the highest tested concentration (49 and 24% of control for plasma and RBC ChE in males and 35 and 27% for plasma and RBC ChE in females, respectively). No significant differences in the levels of ChE inhibition were observed at the different time points (Loeser, 1970).

In another feeding study in the rat, technical methamidophos was administered in the diet to 25 Fischer rats per sex per dose group for up to 56 days at 0, 0.5, 1, 2 and 4 ppm equivalent to 0, 0.03, 0.07, 0.13, 0.24 mg/kg b.w./day in males and 0, 0.03, 0.06, 0.17, 0.28 mg/kg b.w./day in females. The activities of plasma ChE, erythrocyte ChE, butyryl ChE and brain ChE were measured at days 14, 28, 48 and 51. No significant differences in the levels of ChE inhibition were observed at the different time points with the same dose level. The NOEL for inhibition of all the above measured types of ChE was 0.5 ppm, equivalent to 0.03mg/kg/day, based on significant ChE inhibition at 1 ppm (Christenson, 1991)

1.3.2. RAT DERMAL EXPOSURE STUDIES

Methamidophos technical was administered by repeated dermal application to the shaved backs of Sprague Dawley rats (9 or 10/sex/dose). The test substance was applied for three weeks as an aqueous solution (dosing volume of 1 ml/kg b.w.) at nominal doses of 0, 1, 15 or 50 mg/kg b.w./day. The analytically confirmed concentrations (doses) of methamidophos technical in the dose preparations were 0.0, 0.749, 11.2 or 36.5 mg/ml (kg b.w./day)
ChE activity was reduced in both sexes. Moderate reduction of brain (62-59% of controls), RBC (54-45%) and plasma (76-58%) ChE activity was observed at 15 mg/kg b.w. and marked reduction of brain (38-34%), RBC (24-25%) and plasma (33-44%) ChE at the nominal high dose of 50 mg/kg b.w. There was no effect of methamidophos administration on measures of ChE activity at the low dose of 1 mg/kg b.w./day.
In summary, the repeated dermal application of methamidophos produced a dose related inhibition of ChE activity with no other effects of exposure. For both sexes the lowest dosage of 1mg/kg b.w./day did not produce any significant ChE inhibition while the dosages of 15 and 50 mg/kg b.w./day produced moderate and severe inhibition respectively (Sheets *et al.*, 1997).

1.3.3. DISCUSSION OF THE RAT REPEATED EXPOSURE STUDIES

Oral and dermal doses of methamidophos technical producing the same degree of ChE inhibition, were identified in the first feeding study (Loeser, 1970) and in the dermal exposure study (Sheets *et al.*, 1997).

As can be observed from the feeding study in rats (Loeser, 1970), ChE activity at the highest tested dose of 4.57 - 5.58mg/kg b.w./day was reduced to 49-35% of the control value for plasma pseudocholinesterase and to 24-27% for RBC (red blood cells) acetylcholinesterase. From the rat dermal study (Sheets *et al.*, 1997), the highest dose of 36.5mg/kg b.w./day produced a decrease of 33-44% in plasma pseudocholinesterase and 24-25% in RBC acetylcholinesterase. Consequently, the dermal dose of 36.5 mg/kg b.w./day and the oral dose of 4.75 mg/kg b.w./day can be considered as iso-effective and their ratio is equal to 8. This ratio is consistent with the respective value derived from the ratio of the dermal/oral LD_{50} values and it is very close to the dermal/*i.v.* ratio derived from the monkey study. Furthermore, from the above repeated exposure studies, it can be estimated that the degree of methamidophos dermal absorption through rat skin is approximately 16% [given that biovailability is 80% (F) following oral administration, 16%={Iso-EL^4_{oral} [4.57]/(Iso-EL_{dermal} [36.5] x F [80%])} x 100) %] under the experimental conditions of these two studies.

This value is for rat skin and it is well known that it is likely to be significantly higher than the respective dermal absorption for human skin by a factor of up to 10, as was indeed found in the *in vitro* comparative study for doses of the same order of magnitude when expressed as $mg.cm^{-2}$ (van de Sandt, 1998). However, due to lack of critical information related to the pharmacokinetics and metabolism of methamidophos *via* the oral and dermal route *i.e.* possible first pass effect, and the significant differences of these studies from studies specifically designed to determine dermal absorption, *i.e.* duration of exposure, method of administration of the test substance etc, the results are only considered as supplementary (Hakkert, 2001).

Therefore, the PPR Panel considers that this result supports the view that dermal absorption of methamidophos through human skin is significantly lower than 10%.

CONCLUSIONS AND RECOMMENDATIONS

The Scientific Panel on Plant health, Plant protection products and their Residues (PPR Panel), notes that due to the hydrophilic nature of methamidophos, a low absorption rate is expected. The PPR Panel also notes that there are several shortcomings in the available dermal

absorption studies, which do not allow an accurate estimation of the degree of methamidophos dermal absorption through human skin. The low recovery observed in all *in vivo* studies, the possible formation of unstable, volatile metabolites not measured in the respective dermal absorption studies, the possibility of methamidophos hydrolysis on the skin surface prior to absorption, the evidence of side chain metabolites binding to skin proteins, all indicate that monitoring of the radioactivity in the available dermal absorption studies is not representative of just methamidophos but likely includes a metabolite(s) with different properties from the parent molecule. Hence, inclusion of all of the unaccounted radioactivity in these studies in the portion absorbed is not appropriate.

The PPR Panel is of the opinion that data from the study of dermal absorption in monkeys and humans *in vivo*, when compared to those obtained after intravenous injection in the monkey, could serve as a basis for estimating the extent of dermal absorption in humans. This will give a best-estimated dermal absorption of about 5%. The underlying assumption is that the disposition of methamidophos from the monkey study after intravenous injection is similar to that in humans following this route of administration (Miyamoto *et al*, 1988; Smith *et al*, 1977). The value of about 5% is consistent with the 10 % value estimated from the monkey study and the fact that data with a number of compounds indicate a 2-3 fold higher skin absorption in monkeys than in humans (Wester *et al.*, 1976; Wester *et al.*, 1996).
Both monkey and human volunteer studies have been performed with dilutions of the 600 SL formulation (2.39mg/L and 0.72mg/L respectively), which are in the range of the expected field spray concentration (approximately 1mg/L). From the *in vitro* study, with human skin, absorption of the 600 SL formulation was lower (~3-fold) than the spray solution.

DOCUMENTATION PROVIDED TO EFSA

1. Letter from Mr A. Checchi-Lang from the Health & Consumer Protection Directorate-General requesting a consultation EFSA on methamidophos, with ref. E1/DVB D/510472(04), 22 April 2004.
2. Draft Assessment Report (DAR) for methamidophos, Vol. 1, level 1 to 4, p 1-89.
3. Draft Assessment Report (DAR) for methamidophos, Vol. 3 Annex B9 Ecotoxicology, p1-51.
4. Draft Assessment Report (DAR) for methamidophos, Vol. 3 Annex B6 Toxicology and metabolite, p1- 291.

[4] iso-EL: Dose levels, through the dermal and the oral route of exposure, producing the same degree of ChE inhibition.

5. Addendum 1 DAR for methamidophos, Vol. 1, level 2,3 and 4, page 1-55.
6. Addendum 1 DAR for methamidophos, Vol. 3, Annex B, page 2-86.
7. Addendum 2 DAR for methamidophos, Vol.1, level 2 and 3, July 2003, page 1-38.
8. Addendum 2 DAR for methamidophos, Vol. 3 Annex B, July 2003, page 1-89.
9. Comment by Danish authority (EPA) on Evaluation WG meeting 17-18 Sept. 03, ref ABA/STM/11, 26 April 2004.
10. Comment by UK authority (PSD) ref. ASY 58, 16 October 2003.
11. Comment by Swedish authority (KEMI) ref. F-2061-469-00, 20 October 2003.
12. Comment by NL authority following Evaluation WG meeting 17-18 Sept. 03, 6 October 2003.
13. Letter Bayer of 19.3.2004 and enclosures: list of uses supported by available data 11 February 2004.
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**= a conflict of interest was declared to EFSA*

Opinion of the Scientific Panel on Plant health, Plant protection products and their Residues on a request from the Commission related to the evaluation of methamidophos in ecotoxicology in the context of Council Directive 91/414/EEC[1].

(Question N° EFSA-Q-2004-59)

adopted on 14 December 2004

SUMMARY OF OPINION

The Scientific Panel on Plant health, Plant protection products and their Residues (PPR) was asked to review the estimates of avoidance, time spent foraging in treated areas and proportion of contaminated diet obtained in treated areas, and advise on their implications for estimates of acute, short and long term exposure of birds and mammals to the insecticide methamidophos. The PPR Panel concentrated its assessment on the use of methamidophos on potatoes in northern EU Member States in summer as an example. Other uses of methamidophos should be assessed using comparable approaches, which could also be applied to other substances.

The PPR Panel concentrated its assessment on two species considered by the notifier and Rapporteur Member State (RMS), the yellow wagtail (*Motacilla flava*) and wood mouse (*Apodemus sylvaticus*), as they make substantial use of the crops supported for methamidophos. However, the PPR Panel considers that some other species including skylarks (*Alauda arvensis*) and shrews may also make substantial use of the crops supported for methamidophos, and may therefore deserve further attention in the risk assessment. Further species may require consideration when assessing uses of methamidophos on crops in arid areas of the Mediterranean region.

The PPR Panel agrees with the assessment of the notifier and RMS that local populations of wood mice may obtain all of their food from treated fields, based on evidence from radio-tracking studies. The PPR Panel does not agree with the RMS and notifier's assessment that yellow wagtails would obtain only 5% of their food from treated fields after spraying. A detailed review of field observations indicates that yellow wagtails may nest in potato fields and that some individuals may obtain close to 100% of their food within the field. The PPR Panel agrees with the notifier and RMS that use of the field is likely to decrease after insecticide application due to reduced availability of insects, but the potential for exposure immediately after spraying remains because yellow wagtails are known to feed opportunistically on local concentrations of dead insects under some circumstances.

The estimates used by the notifier and RMS for dietary composition for yellow wagtail and wood mouse represent averages between individuals and over time. The PPR Panel notes that

[1] For citation purposes: Opinion of the Scientific Panel on Plant Health, Plant Protection Products and their Residues on a request from the Commission related to the evaluation of methamidophos in ecotoxicology in the context of Council Directive 91/414/EEC, *The EFSA Journal* (2004), 144, 1-50.

this will under-estimate acute exposure of individual animals. Yellow wagtails will take either small or large insects, and are known to feed opportunistically on local concentrations of small insects such as aphids under some circumstances. It is therefore plausible that some yellow wagtails would feed exclusively on small insects after methamidophos applications. Wood mice have wide-ranging diets including seeds, insects and plant foliage, but field data show that during short periods an individual wood mouse may concentrate its feeding on any one of these foods.

In laboratory studies, two quail species, mallard duck (*Anas platyrhynchos*) and the laboratory mouse showed strong avoidance (reduced consumption) of food treated with methamidophos. The notifier and RMS assume that these results can be extrapolated without adjustment to yellow wagtails and wood mice in the field, but the PPR Panel has identified some important factors that could influence the degree of avoidance in the field.

The PPR Panel used a graphical approach to explore the influence of these factors on the exposure of yellow wagtails and wood mice to methamidophos. In the course of these considerations it became apparent that current guidance on how to incorporate avoidance in the estimation of bird and mammal exposure is inappropriate if the avoidance response operates at a threshold dose, as is likely for methamidophos. The PPR Panel developed an alternative approach for assessing the potential role of avoidance. The mechanisms involved are complex and depend upon whether the animal feeds quickly enough to ingest a lethal dose before the avoidance response is manifested. These factors are poorly quantified by currently available data, but it appears possible that both yellow wagtail and wood mouse might feed quickly enough for mortality to occur in field conditions. The PPR Panel identified several options for laboratory or field studies, which could be considered if decision-makers want these risks to be assessed with more certainty.

The PPR Panel briefly considered some other routes of exposure to methamidophos (drinking, dermal exposure, overspray of nestling birds), which were not assessed by the notifier and RMS. Preliminary consideration suggests that, for methamidophos, the risk from these routes may be higher than the risk from dietary exposure.

Key words : methamidophos, bird, mammal, exposure, avoidance, diet, habitat use, PD[2], PT[3], AV[4]

[2] A factor used in pesticide risk assessments to represent the composition of diets eaten by birds and mammals.
[3] A factor used in pesticide risk assessments to represent the proportion of their diets which birds and mammals obtain from pesticide-treated areas.
[4] A factor used in pesticide risk assessments to represent reduction of exposure due to birds or mammals avoiding or reducing consumption of contaminated foods.

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BACKGROUND[5]

Methamidophos is used as an insecticide and is included in the first list of active substances referred to in Article 8(2) of Directive 91/414/EEC[6] concerning the placing of plant protection products on the market. On the basis of the evaluation report prepared by Italy as Rapporteur

[5] Submitted by the Commission
[6] OJ No L 230, 19.08.1991, p.1.

Member State (RMS), the substance has been peer reviewed with Member State experts in the working group "Plant Protection Products – Evaluation" of the Commission. A tripartite meeting with the RMS and the main data supplier was also organised.

The peer review identified several data gaps which were addressed by the notifier. All information submitted has been evaluated and discussed with Member States in the Working groups "Evaluation".

An outstanding issue was identified which needs to be resolved in the risk assessment for birds and mammals.

In the first tier risk assessment, the TER[7] values for the acute and long term exposure scenarios are below the trigger values in the Uniform Principles (Annex VI of Directive 91/414/EEC) of 10 and 5 respectively. According to the Uniform Principles the active substance cannot be included in the positive list of Directive 91/414/EEC without an adequate or refined risk assessment.

Accordingly a refinement risk assessment was carried out according to the *Commission Guidance Document on Risk Assessment for Birds and Mammals under Council Directive 91/414/EEC (Doc SANCO/4145/2000 final of 25 September 2002)*, based on the estimation of avoidance, time spent foraging in treated areas and proportion of contaminated diet obtained in treated areas. On the basis of field studies performed, the notifier concludes that there is not an unacceptable risk for birds and mammals, as toxicity/exposure ratios for birds and other non-target species remained above the trigger values of 10 (acute and short term risk assessment) and 5 (long term risk assessment).

However, certain Member States are of the opinion that such a conclusion cannot be made, due to the limited number of species of birds and mammals observed. Also, it was feared that the repellent characteristics of the substance may have been overestimated and that, consequently, quantities actually ingested by the exposed animals may be higher.

TERMS OF REFERENCE

Will the PPR Panel review the estimates of avoidance, time spent foraging in treated areas and proportion of contaminated diet obtained in treated areas, and advise on their implications for estimates of acute, short and long term exposure of birds and mammals to methamidophos?

ASSESSMENT

1 Introduction

1.1 GENERAL APPROACH TO ESTIMATING EXPOSURE

The refined exposure assessments presented by the Rapporteur Member State (RMS) and the notifier both used the approach recommended in the EU Guidance Document on risk assessment for birds and mammals (SANCO, 2002). Both the notifier and RMS use the following mathematical equation, taken from the EU Guidance Document, to estimate exposure:

[7] Toxicity Exposure Ratio

$$ETE = (FIR / bw) \times C \times AV \times PT \times PD$$ (Equation 1)

where:
ETE = estimated theoretical exposure (mg/kg body weight/day),
FIR = Food intake rate (kg fresh weight/day),
bw = body weight (kg),
C = concentration of chemical in diet (mg/kg fresh weight),
AV = factor to allow for avoidance or repellency (1=no avoidance, 0=complete avoidance[8]),
PT = fraction of food obtained in treated area (number between 0 and 1),
PD = fraction of food type in diet (between 0 and 1).

As there were no direct measurements of the concentration of methamidophos on relevant food types, C was estimated according to the Guidance Document as follows:

$$C = Appl.rate \times RUD \times MAF \times f_{twa}$$ (Equation 2)

where:
Appl.rate = application rate of the pesticide (kg active substance/ha),
RUD = residue per unit dose (extrapolation factors for different foods, specified in Guidance Document),
MAF = multiple application factor (factor to adjust for peak residue after multiple applications, specified in Guidance Document),
f_{twa} = time-weighted average factor (factor to extrapolate from initial residue to the expected average over a longer time period, based on assumptions specified in the Guidance Document).

The PPR Panel's assessment focussed on the derivation of estimates for PT, PD and AV and on their consequences for the estimation of exposure, as requested in the question to the PPR Panel. For other parameters (e.g. C and FIR), the PPR Panel's assessment used the same assumptions as the notifier and RMS, because they were in most cases based on the Guidance Document and the PPR Panel was not asked to consider them in detail.

1.2 SCOPE AND FOCUS OF THE PPR PANEL'S OPINION

The PPR Panel did not undertake a comprehensive assessment covering all uses of methamidophos, but instead focused on example scenarios to address the issues raised in the question from the Commission. The PPR Panel recommends that its approaches should be considered when assessing other scenarios both for methamidophos and other pesticides.

The crops supported for methamidophos were potatoes (with slightly different use patterns in northern and southern EU[9]), flowering brassica/cabbage in northern EU, maize in southern EU, and ornamentals in glasshouses. The PPR Panel focused mainly on the use in potatoes in northern Member States as an example, since one of the field studies submitted by the notifier was conducted in potatoes in Germany. The specific use pattern considered was for up to 5 applications to potatoes at 0.72 kg a.s./ha, with a minimum 10 day interval between applications, because this was the use considered in the latest draft of the RMS's Draft Assessment Report[10]. The PPR Panel also comments briefly on special factors affecting exposure in arid regions of the southern EU.

[8] Note that in some cases, consumption of treated food in dietary studies can exceed consumption of untreated food, implying AV>1 (Luttik, 1998).
[9] "Northern" and "southern" are not defined by either the notifier or RMS. For the purposes of this opinion, northern was considered to include Germany, and southern to include Italy and Spain.
[10] Draft Assessment Report, Addendum 2, vol 3, annex B, page 52. Separate information from the notifier indicated that the typical timing of this use in Germany is June. Modifications including reduced application

The notifier and RMS focused their refined assessments on wood pigeon (*Columba palumbus*) and yellow wagtail (*Motacilla flava*) as relevant bird species, and wood mouse (*Apodemus sylvaticus*) as a relevant mammal, based on the notifier's field studies and other information. The PPR Panel focused primarily on the yellow wagtail and wood mouse as examples, but also considered more briefly the potential relevance of other species including some that were not observed in the notifier's studies.

The refined assessments presented by the notifier and RMS consider acute and long-term risks to birds, and acute risks to mammals. Both the notifier and RMS argue that an avian short-term assessment and mammalian long-term assessment are unnecessary. The PPR Panel focused primarily on acute exposure but also considered more briefly the potential significance of longer timescales.

It is important to define the population (e.g. local, regional, national) for which exposure and risk is to be assessed. The Guidance Document (SANCO, 2002) notes that the persistence and abundance of populations may be more relevant endpoints than the responses of individual organisms, but also states that "appreciable mortality without population consequences may be judged unacceptable". Therefore the PPR Panel considered the assessment of exposure at two levels: for local populations (defined as those animals visiting treated fields at least occasionally) and for the worst-case (most exposed) individuals (because if their exposure is low then "appreciable mortality" can be excluded). The potential consequences on wider spatial scales (regional, national) are discussed more briefly.

2 Time spent foraging in treated areas (PT)

2.1 INTRODUCTION

The EU Guidance Document (SANCO 2002) recognizes that it is difficult to obtain reliable estimates of PT. Most fundamentally, the way PT is used in Equation 1 implies that it is the *fraction of the diet* (in terms of fresh weight) that is obtained in treated areas, but in practice this would be extremely difficult to measure directly in the field. Therefore, estimates of PT are usually based on information concerning the *fraction of time* spent by the animals in treated crops, although there are several reasons why the fraction of diet obtained in treated crops may not be equal to the fraction of time spent there (SANCO 2002, p. 30).

Other difficulties in estimating PT include:

- Most available studies focus on estimating use of a single study field, but this may underestimate exposure because some birds and mammals range over multiple fields, of which more than one may be treated with the same pesticide.
- When animals spend a lot of time close to the field edge, it is difficult to determine (by observations or radio-tracking) how much is spent inside or outside. Also, it may be necessary to distinguish time spent in the drift zone, so as to estimate how much this contributes to exposure.
- Visual observations will be biased if visibility is poor, or differs significantly between crops and other habitats.
- Visual observations of unmarked animals cannot determine the distribution of PT between individuals, and can only estimate the average if the size of the local population is known.
- Both visual observations and radio-tracking may be biased if the activities of the observer cause disturbance and alter the behaviour of the animals.

rates have been proposed by the notifier, and could be assessed by suitable adjustments to the PPR Panel's calculations and figures.

- For both visual observations and radio-tracking, it is important to consider the relation between the studied animals and the population of interest for the assessment (e.g. animals caught outside the crop may use it less than those caught inside).
- General ecological knowledge may help but is very qualitative and, on its own, provides little certainty about the true value of PT for specific crops and conditions.
- Field studies may not be representative of the same crop on other sites, or at other times of year, or in other years. Even if the choice of sites and times is appropriate, there may be substantial sampling uncertainty if the number of study sites and times is low.
- Use of a field may change sharply after applications of insecticide or herbicide, if it reduces the availability of foods used by the species of interest.

Most of these difficulties are encountered in the field studies submitted by the notifier for the assessment of methamidophos (see evaluation in Appendix 1), and are taken into account in the PPR Panel's assessment (next section).

2.2 ESTIMATION OF PT FOR METHAMIDOPHOS

Yellow wagtail – local populations

The PPR Panel considered carefully how the various pieces of information available from the notifier's field studies (Appendix 1) and other published sources could be used to develop estimates of PT for yellow wagtail during June (the period when methamidophos is used on potatoes in Germany), while taking account of the associated uncertainties.

In census observations, yellow wagtail was the third most frequently observed bird species inside the potato fields, and also the only species seen more frequently inside the field (average 0.58 birds per census over 4 sites and 3 time periods, or approximately 9 birds/km^2) than in the surrounding habitat (0.50 per census). The proportion of observations that were inside the fields was higher in the earliest census period (closest to the time of methamidophos use in Germany). These numbers and those in the notifier's "whole-day observations" (Table 1) are consistent with densities of yellow wagtails reported in other studies (e.g. range 0-4.6 pairs/km^2 in a range of agricultural habitats and 4.4 pairs/km^2 in potatoes; Mason & MacDonald, 2000). The yellow wagtail was also one of the 3 most frequently observed species in tomato fields, and yellow wagtails were confirmed to be nesting inside the tomato fields.

The PPR Panel regard the notifier's "whole-day observations" as providing the strongest line of evidence for yellow wagtail, due to the consistency of numbers over time and between fields (Table 1). These results might represent the continuous presence of a small number of resident breeding birds, each with PT close to (or even equal to) 1. On the other hand, they could result from a series of shorter visits by a larger number of different individuals, in which case PT for each individual could be close to zero. Without data from marked birds or radio-tracking, it is not possible to be certain which of these interpretations is true. The PPR Panel considers that the most probable interpretation is that, in those fields where this species is present (2 of the 4 potato fields and all the tomato fields) there is a small population of birds with territories centered in the field and an average PT of approximately 0.4-0.6 (using the ratio of maximum to mean number of observations as an "impression": Fletcher & Greig-Smith, 1988). It is striking that closely similar values of this ratio were obtained for all 6 of the fields shown in Table 1. However, this ratio is a very uncertain estimate of PT, because birds were unmarked and visibility in the crop was limited[11]. Furthermore, it should be remembered that PT for individual birds could range from close to zero (for visiting non-residents) to one (based on the

[11] Potatoes: 90% cover, height 50-75cm in the study period.

available evidence it cannot be excluded that some birds stay entirely within the crop on some days).

Table 1. Numbers of yellow wagtails recorded in whole day observations.

	Potatoes (Germany)		Tomatoes (Italy)			
Field no.	3	4	1	2	3	4
Date/time	19 July	22 July	22 June	24 June	23 June	25 June
6:00	2	4	2	1	2	2
7:00	1	5	2	1	2	2
8:00	3	3	2	2	3	2
9:00	2	3	3	2	2	2
10:00	0	5	4	1	2	1
11:00	3	2	2	2	2	1
12:00	2	4	3	2	4	1
13:00	2	4	3	0	3	2
14:00	3	0	1	2	2	1
15:00	1	0	3	1	2	1
16:00	0	1	3	0	2	2
17:00	1	1	2	0	2	1
18:00	0	0	2	3	1	1
19:00	1	0	2	1	2	1
20:00	2	1	2	3	2	0
21:00	1	1	2	1	2	0
Mean	1.5	2.1	2.4	1.4	2.2	1.3
Maximum	3	5	4	3	4	2
Mean/max	0.50	0.43	0.59	0.46	0.55	0.63

Note: Yellow wagtails were not observed at any time in similar observations at two additional potato fields in Germany (not shown). The ratio of mean to maximum is an approximate estimator for the proportion of time spent in the study field, averaged over the population using the field. See text for discussion of important biases and uncertainties affecting these estimates.

An alternative but less probable interpretation of the whole-day observations is that they reflect a larger population of birds with territories centered outside the field, making short visits to the field. This would imply a high turnover with different birds seen every hour. PT cannot be estimated precisely without knowing the turnover rate (which cannot be known with unmarked birds), but could be anywhere between 0.4 (if turnover is low) and close to zero (e.g. 0.05 or less, if turnover is high). The PPR Panel considers this interpretation much less probable than the one in the preceding paragraph, because it is less compatible with (a) the consistency of numbers from hour to hour and field to field, (b) the lack of a large population in the surrounding habitat in the census observations, (c) the results of surveys of yellow wagtails in potatoes and other crops in the UK (Mason & MacDonald, 2000), (d) the finding that yellow wagtails were nesting inside the field, at least in the case of tomatoes, and (e) more weakly, the lack of observations of wagtails entering and leaving the field[12].

It is important to consider how the timing of the notifier's studies affects the interpretation of PT. For potatoes in Germany methamidophos is typically applied in June (no information for other crops and regions) but the study on potatoes in Germany started in mid-July, whereas the main breeding period of yellow wagtails in Central Europe extends from mid-May to the first

[12] Blackbirds were described by the notifier as "often moving between the fields and adjacent wood habitats". No such remark was made for yellow wagtails, which should be more conspicuous because of their colour.

week of June (Glutz von Blotzheim, 1985). Therefore, during the period when methamidophos is used, (a) the number of yellow wagtails breeding in the fields may have been higher, and (b) their foraging ranges might have been smaller (more focused around the nest). Both these factors would tend to increase PT, but by what extent is uncertain.

All interpretations of the field observations are affected by the fact that the proportion of time spent in the crop (let us call this PT_{time}) will not be precisely equal to the proportion of diet obtained there (PT_{diet}), and might be very different. Anecdotal reports from the literature indicate that at least some yellow wagtails, in some circumstances, do much of their feeding outside their nesting territories (Glutz von Blotzheim, 1980, Dittberner, 1984). This might apply to some of the birds nesting in the crops considered here, reducing PT_{diet}. On the other hand, it is also possible that PT_{time} underestimates PT_{diet}, for example if birds left the field for other purposes (e.g. to obtain water), or if the rate of ingestion (g/min) is lower off-field. The PPR Panel concludes that the uncertainty about the relation between PT_{time} and PT_{diet} might increase average PT_{diet}, but is slightly more likely to reduce it.

Both the interpretations above are further affected by the fact that application of methamidophos will reduce both the availability and palatability (Stafford *et al*. 2003) of insects for birds. However, the extent of the reduction in insect populations after spraying is variable and the rapidity of its onset is uncertain[13]. On the one hand, wagtails might cease feeding in the fields almost immediately, in which case PT would be reduced to zero. On the other hand, yellow wagtails are known to feed on local concentrations of both live and dead insects[14]. The PPR Panel considers it plausible that yellow wagtails might continue to feed in the field for much of the day of spraying, so that average PT for the local population might still be around 0.5 for the purposes of acute exposure assessment[15]. Over longer periods (>1 day) a substantial reduction of PT seems more probable although, if yellow wagtails are nesting in the crop, it seems likely that they will still forage there to some extent so long as any prey are available.

Extrapolation of the above conclusions from potatoes and tomatoes to other crops is uncertain, although surveys in the UK shows similar densities (around 4 territories per km^2) of yellow wagtails in potatoes, maize (another supported use of methamidophos), salad crops, beans and peas (Mason & Macdonald, 2000). In agricultural landscapes the main habitat of yellow wagtails used to be pastures, but in recent times (1960-70s) the species shifted more towards arable crops including potatoes, beet, cereals and others (Glutz von Blotzheim, 1985). In Denmark, Møller (1980) found yellow wagtails in grass fields but not in potato fields. In northern Spain, yellow wagtails have been appearing in areas of arable crops where they were not recorded before (Alvarez *et al.*, 1998). Further information from Spain suggests that, in more arid parts of southern Member States, irrigated crops may be a strongly preferred habitat for yellow wagtails, with few alternative sources of food (Marti & Moral, 2003, Palomino, 2004, Cantos & Asensio, 1989). This is likely to mean that average PT prior to insecticide application would be higher in these conditions. It could also mean that the reduction after spraying would be less. On the other hand, birds might switch their foraging to other irrigated crops nearby if these were not sprayed simultaneously.

[13] It appears there is remarkably little published information on this. A study of normally-sprayed spring barley fields in Denmark showed biomass densities of arthropods reduced to 36% of untreated controls during the 14 days following insecticide application (95% CL 21-51%, n= 4 fields for 4 years, Odderskaer *et al.*, 1977).

[14] There are 2 reports, from different countries, of yellow wagtails feeding on dead insects (mayflies) when present in high densities, and they have also been reported to feed on outbreaks of live insects, e.g. aphids on trees or thistles in pasture (Dittberner, 1984).

[15] The spraying operation itself would cause some disturbance and might cause birds to leave the field. However, the PPR Panel considers that this will have little effect on PT for yellow wagtails as they are likely to be nesting in the field and can be expected to return after a short period.

Most of the above assessment relates to average PT for those birds that visit treated fields. After considering all the factors, it remains possible that PT for individual birds could range from close to zero (for visiting non-residents) to 1 (because it cannot be excluded that some individuals might continue to feed entirely within the crop after spraying).

The PPR Panel concludes that:

- PT for the most-exposed individuals might be as high as one, because yellow wagtails sometimes feed on concentrations of dead insects
- Average PT for yellow wagtails resident in the field, on the day of spraying, is affected by a number of substantial uncertainties but could plausibly be as high as 0.5. This is based on: whole-day observations suggest that average PT in late June to mid July, in the absence of spraying, may be around 0.4-0.6; somewhat higher values might be expected earlier in the season, when methamidophos is used; PT_{diet} could be either higher or lower than PT_{time}; insecticide application will reduce the availability of live insect prey substantially within minutes of spraying, but wagtails may continue to feed on dead insects for several hours.
- Average PT for yellow wagtails resident in the field may be significantly reduced over longer periods, because insects killed by spraying will become depleted or unpalatable and live populations may take some time to recover.
- PT for yellow wagtails in arid regions of southern Member States may be significantly higher than other areas because of the lower availability of alternative foraging habitat.

These conclusions are summarised in Table 2. The PPR Panel's assessment for acute exposures contrasts strongly with the figure of 0.05 used by the notifier and RMS[16].

Table 2. Summary of the PPR Panel's assessment of PT for assessing exposure of yellow wagtails to the proposed uses of methamidophos in potatoes.

	Plausible worst case for PT
Acute exposure (1 d): most-exposed individuals	Up to 1
Acute exposure (1 d): average for birds resident in treated fields	Around 0.5
Longer term exposure (>1 d): average for birds resident in treated fields	Less than 0.5, depending on reduction and recovery of insect populations
Exposure in arid regions of southern Member States	Probably greater than in other areas.

Note: Estimates in the Table relate to those fields where yellow wagtails are present (e.g. 2 of 4 fields in the notifier's potato study, and 4/4 in the tomato study). Similar estimates would apply to similar uses of other insecticides, but different considerations apply for non-insecticidal products (see text for details).

The PPR Panel notes that the average PT is of limited use for risk assessment. What is really needed is the *distribution* of PT, so that the *proportion* of individuals experiencing lethal exposures can be estimated. Distributions of PT can only be obtained from observations or radio-tracking of individual animals. When such data are lacking, average PT may be helpful in indicating whether substantial mortality is expected, but this should be interpreted with caution, and the possibility of mortality should not be discounted without considering estimates for the most-exposed individuals[17].

[16] The notifier and RMS state that PT=0.05 is supported by the fact that only 5% of all bird observations were made within the crop. However, this statistic combines their data for all species including many seen only outside the crop; it is therefore inappropriate as an estimate for yellow wagtail. They also give more weight to the effect of insecticide in reducing insect availability, and ignore the possibility of foraging on dead insects.

[17] Mortality may occur even if the average is well below lethal levels, as the distribution of PT can be highly skewed (e.g. Crocker et al. 2002).

The PPR Panel notes that the assessment in Table 2 could apply to other insecticides used on these and similar crops in the period when yellow wagtails are breeding. A modified assessment would apply for non-insecticidal products, because they would cause neither a short-term abundance of dead insects, nor a longer-term reduction in live insects.

Because the estimation of PT is very uncertain, the PPR Panel explores below (section 5) its influence on the overall estimates of exposure and risk for the yellow wagtail.

Yellow wagtail – wider populations

Estimating exposure in wider populations (e.g. local, regional, national) is difficult and depends heavily on (a) the scale of the population considered, (b) the proportions of different crops in the landscape, (c) the proportion of each crop that is treated, (d) the pattern of treatments in space and time, and (e) the preference of each species for each type of crops (if this is high, PT can be high even if few fields are treated).

Very approximate assessments for wider populations can be made using simple assumptions. For example, Barfknecht (2003a) reports that the rotation in the region of the potato study comprised potatoes for 1 year in 3. Based on this information it might be reasonable to assume that, each year, about one third of the fields are cropped with potatoes. This is loosely compatible with the numbers of additional fields shown in maps of the study sites. If authorised, methamidophos could potentially be used on every field of the supported crops. This is obviously unlikely on a national scale, but for a local population (e.g. covering several farms) it may be a reasonable worst case to assume all potato fields are treated within a few days, because in some years all fields might be infested at about the same time. If, on this basis, it is assumed that one third of the local landscape comprises potato fields treated with methamidophos, and that the density of yellow wagtails is similar in potatoes and other crops, then the values in Table 2 would be relevant to about one third of the local population. In fact, the proportion would be lower than one third, because not all potato fields contain yellow wagtails (see Table 1) and not all are treated with methamidophos. For the remainder of the population, that do not visit potato fields at all, PT would be zero[18] (assuming other crops are not treated). For regional and national scales the proportion of birds exposed might be further decreased due to the inclusion of increasing areas where treated potatoes are absent.

Other species

The PPR Panel recommends that a full risk assessment should include similarly detailed consideration of PT for other species with potentially high exposure, and offers the following observations as a starting point.

Woodpigeon. This was the second bird species considered in the notifier and RMS assessments. It was the species most frequently seen overall in censuses in the potato fields in Germany (1.17 birds/census), although it was more often seen in surrounding habitat (4.33 birds/census[19]), and in the first census period, only 1 bird was observed on-field. In the 2 days of whole-day observations on 4 fields, only 2 woodpigeons were observed, in 1 hour on one field. This suggests that during the earlier period, closest to insecticide use, woodpigeon use of these particular fields was very limited. Woodpigeons were not observed at all in the notifier's study on tomatoes, although the normal range of this species extends into northern Africa. These observations suggest that PT for woodpigeon for these areas and crops is very low. However, several complications need to be considered. First, woodpigeons have very large

[18] Note that it would be misleading to average PT over wider populations, because this may give the impression that all animals experience low exposures. Instead, we estimate the proportions showing different levels of PT.
[19] The study report incorrectly gives this figure as 2.08 due to an arithmetical error in notifier's Appendix 11.

foraging ranges (10-20km from the nest; Glutz von Blotzheim, 1985; Cramp, 1988), so the individuals visiting the study fields may also have visited other potato fields on the same day. Second, in some countries[20] at least, woodpigeons tend to be very wary of humans; observers walking around the field every hour would probably scare birds away. For these reasons, the notifier's studies may under-represent PT for this species. In addition, other species of this family (Columbidae) may be more relevant in some regions, e.g. *C. livia*, *C. oenas* and *Streptopelia decaocto* are more frequent than wood pigeon in irrigated fields in the central area of Spain (Moral *et al*,. 2002).

Skylark. In the notifier's censuses in Germany, skylarks (*Alauda arvensis*) were seen less often in the potato fields (0.25 birds/census overall) than in the surrounding habitat (1.58 birds/census). However, in the whole-day observations in July they showed a similar pattern to yellow wagtail on one of the 4 study fields, where 1-4 skylarks were observed in 10 of the 16 hourly observations. Skylarks were not recorded in the Italian tomato fields. However, in UK surveys this species was found in potatoes at higher densities than yellow wagtail, and in maize at similar densities to yellow wagtail (Mason & Macdonald 2000). Also in the UK, radio-tracking studies have shown that some skylarks spend virtually all their time (>90%) in arable crops[21] (Crocker *et al.*, 2002). These data suggest that skylarks deserve similar attention to yellow wagtail in the assessment for methamidophos, especially as their partly herbivorous diet (section 3) may make them more likely to continue foraging in the field after insecticide application[22].

Other bird species. Other species of birds appear to have made less use of the potato and tomato fields in the notifier's studies, when compared to yellow wagtail and skylark. Blackbirds (*Turdus merula*) were the second most frequently observed bird species in the potato fields (0.83 birds/census overall) but were more frequent in the surroundings (2.58 birds/census) and were often seen moving between field and woods, suggesting they may have been nesting in the adjacent habitats rather than in the potato fields. Tree sparrow (*Passer montanus*) was the bird species most frequently observed in the tomato fields (2.25 birds/census over all time periods), although this was influenced by a single high count (17) and much higher numbers were seen in the surroundings (average 25.5 birds/census). In the first set of whole-day observations, tree sparrows were recorded in moderate numbers (up to 13) throughout most of the day on tomato fields 1 and 4. Given the relatively high local populations of this species, it is likely (but not certain) that these numbers represent a series of visits by different birds rather than a small number present continuously. House sparrows (*Passer domesticus*) were observed as frequently in tomato fields as yellow wagtails (1.58 birds/census) but much more often in the surroundings (18.75 birds/census). However, unlike wagtails and tree sparrows, house sparrows were only sporadically present during the whole-day observations on tomato fields. Furthermore, house sparrows were most numerous at tomato sites 1 and 2, and may have been feeding mainly at nearby poultry and pig rearing units.

The notifier's study in tomatoes was intended to be representative of conditions in Southern European Member States, but was conducted in a northern part of Italy where the climate is not representative of the wider Mediterranean region (EEA, 2003). More southerly sites are more dependent on irrigation, and wildlife there may make more use of the cropping area than is indicated by notifier's study (Appendix 1). Furthermore, the diversity of bird species, especially small insectivorous species, was lower than expected for agricultural areas with small fields in the Mediterranean region (Ceballos & Purroy, 1981; Moral *et al.*, 2002; Martí & Moral 2003).

[20] This is true in the UK, probably because woodpigeons there are a preferred quarry of hunters.
[21] In the published account of this study, time spent in crops is given as a total and not subdivided between crops.
[22] Unlike insect prey, the availability of plant material will not be decreased by the insecticide. Also, pesticide residues may be higher on foliage than insects, as is assumed in EU screening assessments (SANCO, 2002).

Therefore, a full assessment should examine the possibility that additional species with higher PT may be found in irrigated crops in the Mediterranean region.

Wood mouse. The notifier's trapping results show wood mice were present at all 4 potato fields. Of 4 individuals that were radio-tracked, one spent no time in the potatoes and the other 3 were reported as spending 62%, 62% and 83% of their time in the potatoes[23]. The true percentages are probably higher, as it is probable that part of the time attributed to "changing habitat" and "animal not observed" was actually spent in the potatoes. In the tomato study, 8 individuals were radio-tracked. For the 3 animals that were caught inside the cropped area, the percentage of fixes that occurred in the crop was 79%, 100% and 100% respectively. For the 5 animals caught in the surroundings, the percentage of fixes that occurred in the crop was 4%, 49%, 78%, 89% and 91% respectively. The average speed of movement of radio-tracked animals was estimated at 30m/h in tomatoes, 10m/h in surrounding habitat and 51m/h when changing habitat, but this has implications for the assessment of PD (see section 3) more than PT[24]. Overall, the data imply that PT=1 for the most exposed wood mice in potatoes and, probably, also in other crops on which the use of methamidophos is supported. The average PT for those mice that are resident in the crop might be around 80% (e.g. the average percentage of fixes in-field in the notifier's tomato study was 79%, ignoring the two animals which scarcely used the field at all). In a complete assessment the uncertainties affecting these estimates should be considered in more detail. However, it is noted that wood mice are less likely than yellow wagtails to reduce PT after spraying due to reductions in insect availability, partly because of their more limited mobility and partly because their diet includes a proportion of other food (the notifier and RMS assume 70% seeds) which may increase after spraying.

Other mammals. Seven bank voles (*Clethrionomys glareolus*) were radio-tracked in the potato study but none spent any time in the potato crops (all were caught in surrounding habitat). Savi's pine voles (*Microtus savii*); they were caught only at the border of the tomato fields and none of the 4 individuals radio-tracked spent any time in the tomato crops. No shrew species was caught or seen on any of the potato fields but trapping method may have under-represented them. Two lesser white toothed shrew (*Crocidura suaveolens*) were found dead during the tomato study. Shrews deserve more attention in the assessment of methamidophos, as their small body size, high metabolic rate and insectivorous diet could make them more exposed than wood mice. The notifier made only incidental observations of larger mammals, which provide no indication of how much time they spent in the crops. Rabbits (*Oryctolagus cuniculus*) "were observed frequently entering potato fields" and brown hare (*Lepus europaeus*) was observed in one potato field and two tomato fields. There was evidence of hedgehogs (*Erinacus europaeus*) inside two tomato fields and in the surroundings of a third. A full assessment would need to rely primarily on information from the general literature to estimate the exposure of larger mammals. In addition, as for birds, a full assessment should examine the possibility that additional species with higher PT may be found in irrigated crops in the Mediterranean region.

3 Composition of diet obtained in treated areas (PD)

3.1 INTRODUCTION

The Guidance Document (SANCO, 2002) defines PD as "fraction of food type in diet (between 0 and 1)". It is implicit, in the standard equation for estimating exposure (Equation 1 in Section

[23] Three of the four wood mice radio-tracked in potatoes were caught in the crop: the one caught outside spent 62% of its time in the potatoes when tracked.

[24] The legend to Table 13 states 'the speed to cross the tomato fields were almost as high as the "changing habitat" speed indicating that wood mice do not search for food on tomato fields'. This overstates the similarity of speeds and is not compatible with the finding that 2 animals had 100% of their fixes in the tomatoes.

1.1), that the "food type" refers to food which contains pesticide residues at level C, and that PD refers to the intake of this food type inside the treated area as a proportion of the total food intake inside the treated area, i.e. the composition of diet obtained in treated areas.

In reality, animals may eat several food types with differing residue contents. For refined assessments where multiple food types are considered, the Guidance Document (page 32) replaces Equation 1 with:

$$ETE = \sum((FIR_i / bw) \times C_i \times AV_i \times PT_i \times PD_i) \quad \text{(Equation 3)}$$

and slightly changes the definition of some of the terms:
ETE = estimated theoretical exposure (mg/kg body weight/day), summed over food types (food type i=1, 2, 3 etc),
FIR_i = daily uptake of fresh material (kg fresh weight/day) an animal would require if it were feeding exclusively on food type i,
bw = body weight (kg),
C_i = concentration of chemical in food type i (mg/kg fresh weight),
AV_i = factor to allow for avoidance or repellency of food type i (1=no avoidance, 0=complete avoidance),
PT_i = fraction of food type i obtained in treated area (number between 0 and 1).

The Guidance Document points out (SANCO, 2002, page 32) that, in this version of the equation, PD_i is strictly the proportion of the daily energy requirement that is comprised of food type i, but suggests that this is closely approximated if PD_i is estimated as the proportion of the daily food intake in dry weight that is comprised of food type i. This approximation will be fairly close for diets comprising of food types with similar energy contents, and Annex 1 of the Guidance Document quotes values in the range 18-22 kJ/g dry weight for most food groups (an important exception being dicotyledonous crop leaves, 11.2 kJ/g dry weight).

Although the notifier and RMS quote Equation 1 when assessing mixed diets for the yellow wagtail and wood mouse, which would be inappropriate, they actually used Equation 3.

There are extensive published data on diet composition for many species of birds and mammals obtained mainly by analysing samples of gizzard contents, stomach contents or faeces, and in a few cases by direct observation or filming of feeding behaviour. A number of difficulties arise in using these data to estimate PD. These include:

- results are often reported as percentages in terms of volume, weight or number of items, introducing uncertainty when extrapolating to energy or dry weight,
- stomach and especially faecal samples may underestimate the frequency of more digestible food types,
- diet composition depends on availability of food for the area and time of the study (e.g. some bird species change their diet markedly when nesting or moulting) so it is necessary either to select the data that are most relevant to the crops and periods being considered, or to extrapolate between diets in different conditions,
- results are often reported pooled over study animals, so information on dietary variation between individuals is lost. This can be important: e.g. a pooled PD of 0.5 could imply at one extreme that every individual has PD=0.5, or at the other extreme that half the individuals have PD=0 and half have PD=1.

Finally, data on diet composition usually relate to the overall diet, and not to the diet in specific parts of the habitat. Because of the way equations 1 and 3 are constructed, using overall diet data to estimate PD implies an assumption that the composition of the diet is the same in treated and untreated habitats. The PPR Panel is unaware of any data to test this assumption,

which may be invalid (e.g. when insecticide or herbicide use alters the availability of insects and plants in the treated area). This could bias the estimate of exposure and requires consideration when estimating PD.

3.2 ESTIMATION OF PD FOR METHAMIDOPHOS

The PPR Panel considered the estimation of PD only briefly and for selected species, to illustrate the issues involved. A full assessment should conduct a more comprehensive search of relevant literature (e.g. ornithological publications in different Member States) for all the relevant species.

Yellow wagtail

The yellow wagtail is generally regarded as exclusively insectivorous. For the purposes of this assessment, the key questions are what proportions of these insects are "small" and "large", and what proportions are taken from the ground and from the vegetation, as lower levels of residues are expected in larger insects (because they have a low surface area to volume ratio) and in those taken from the ground (due to interception by the crop). Observations made during the notifier's study for tomatoes in Italy showed that at least some insects were taken from the ground, but are insufficient to estimate the proportion of ground feeding with any certainty (see Appendix 1 for details).

Published data on dietary composition of yellow wagtails were reviewed by Cramp (1988). A very wide range of invertebrate prey has been reported by various authors. The composition of the diet has been quantified in a number of studies, some of which are summarised by Cramp (1988). One of the most recent (Davies, 1977) gives information on the types and sizes of insects taken by yellow wagtails feeding at dung pats in pasture near Oxford, UK. For these birds faecal samples contained almost wholly Diptera: 667 items included 44% (by number) Sphaeroceridae (1-4mm long), 35% Scatophagidae (5-10mm), 6% beetles (1-3mm). Larger Sphaeroceridae (3-4mm) were taken preferentially (41%), when compared to their prevalence at the dung pats (10%) but Scatophagidae (5-10mm) were selected against (77% of available insects but only 35% in faeces). It is unknown whether the Scatophagidae were selected against because of their larger size, or some other characteristic. In the same study, faecal samples from yellow wagtails feeding by pools in pasture, in May, showed a preference for Drosophilidae (18% in trap samples but 44% in faeces, size 2-3mm). Of course, it is difficult to extrapolate preferences from dung pats and pools to potatoes and other crops, where the invertebrate fauna will be very different. All that can be said is that in some circumstances wagtails show preferences for Diptera in the region 3-4mm (perhaps qualifying as "large" insects[25]), and in other circumstances for Drosophilidae in the region 2-3mm (probably qualifying as "small" insects). Cramp (1988) also quotes composition data from studies in the former USSR and Nigeria, and cites without details further studies published between 1909 and 1978. These studies may be less relevant to the supported crops, but this should be checked for a comprehensive assessment.

Dittberner (1984) cites several instances of yellow wagtails feeding exclusively for hours, or maybe days, on outbreaks of aphids on trees or thistles in pasture, and two reports, from different countries, of yellow wagtails feeding on dead insects (mayflies) when present in high densities. These observations suggest that yellow wagtails are opportunistic foragers, and

[25] There is nowhere a direct definition of "small" and "large" insects. The Guidance Document only says that "small birds are assumed to prefer small insects". The original proposal for the distinction (Kenaga, 1973) implies that "large" insects should be those for which the surface area to volume ratio is similar to cereal grains. This suggests that insects of 3-4 mm could be regarded as "large", although the surface area to volume ratio is actually much higher for the insects because of their more irregular shape.

make it conceivable that they might concentrate their feeding on pest insects – including small insects such as aphids – during outbreaks before insecticide application, and on dead insects after insecticide application. Therefore, it is plausible as a realistic worst case that their diet in some treated fields could comprise entirely small insects (PD_i = 1 for small insects). However, if the yellow wagtail's foraging is opportunistic, it is equally plausible that they could forage entirely on large insects in other treated fields (PD_i = 1 for large insects). All intermediate values between these extremes are also possible. The average PD_i for a population covering multiple fields is unlikely to be close to zero or close to one, but cannot be estimated more precisely with the available information. Therefore, the PPR Panel explores below (section 5) its influence on the overall estimates of exposure and risk for the yellow wagtail.

Over a longer term exposure, one might expect intermediate values of PD reflecting more closely the availability of different insect types in the field. The notifier and RMS assumed wagtails eat 50% small insects in their acute assessment, but only large insects in their long-term assessment. The justification for this is unclear, as the only difference in their arguments for the two assessments is that one sentence in the acute assessment ("Ground dwelling species are furthermore less exposed to sprayed pesticides due to plant interception if the crop is well developed") is omitted from their long-term assessment.

Wood mice

The wood mouse is generally considered as primarily a granivore, although it also takes both foliage and animal matter.

The notifier's study in tomatoes reports the stomach contents of 17 wood mice caught by snap-trapping. The results are summarised in Table 3 (in Appendix 1). Although several types of foods were recorded altogether, 12 of the 17 mice contained only one identifiable type of food. This suggests that while as a population the diet was mixed, over short periods (e.g. one bout of feeding) many mice concentrated on a single food type (PD_i=1 over short periods). Amongst these were individual mice that contained only insects, or only green parts of plants. Six mice contained only seeds, corn or starch, which the notifier commented could have been obtained from a nearby farm with pigs and poultry.

The notifier and RMS refer to Rogers (1989; *cited* in Rogers & Gorman, 1995) for data from wood mice living in oil seed rape fields in the UK, where animal material comprised 70% of the diet. They assume that a similar proportion will apply in the supported crops for methamidophos, and that the remaining 30% of the diet will be made up of seeds. Niethammer & Krapp (1978) reported that the stomachs of 40 wood mice caught in central Germany between March and July contained 66% seed and 34% green plant (by volume; the habitat in which these mice were caught is not stated). Pelz (1989) reported stomach contents of 346 wood mice trapped over 7 years on arable farms in Rhineland, Germany. Those caught in June contained 32% cereal grain, 25% dicotyledenous seeds, 25% insect larvae, 9% earthworms and 9% vegetative plant tissue.

The results from the literature and the notifier's study in tomatoes suggest that vegetative plant tissue is a normal though not primary component of the wood mouse diet. The notifier and RMS argue that contaminated leaves will not be taken after spraying because they contain higher concentrations of methamidophos and will be avoided by wood mice. However, the expected concentration on leaves is 94 mg a.s./kg[26] which, using their fitted equation for the feeding study with wood mice, implies AV of 0.64. This does not seem sufficiently low to rule out consumption of contaminated leaves, especially during the first bout of feeding after

[26] Based on application rate = 0.72 kg a.s./ha; with RUD = 87 and multiple application factor MAF = 1.5 as assumed by the notifer and RMS.

spraying (see section 5), and in any case should be accounted for in the assessment of AV rather than PD to avoid double-counting of the avoidance response.

Leaving aside the issue of vegetative material, the data show variable results with regard to the relative prevalence of animal matter and seeds in the diet with a ratio of 70:30 in one study (as assumed by the notifier and RMS) but approximately the reverse in two other studies. It can be expected that the actual contribution of these materials will vary from site to site according to local conditions. Furthermore, it is likely (and supported by the notifier's results in Table 3) that over short periods of time (e.g. a single bout of feeding), individual wood mice may concentrate (PD_i=1) on any one of these food types (insects, seeds or vegetative material). These possibilities are considered further in section 5 below.

4 Avoidance (AV)

4.1 General issues concerning the assessment of avoidance

Avoidance as measured in feeding studies with chemicals can be a combination of several different responses including (a) a reduction in the rate of feeding due to novel or unpleasant characteristics of the contaminated food (e.g. taste or odour) and (b) complete cessation of feeding due to the onset of intoxication.

In Equation (3), AV_i is a multiplicative factor representing the proportionate reduction of consumption of food type i. The notifier and RMS use regression analyses of the relationship between AV and C in feeding studies to estimate the degree of avoidance expected for each food type based on their estimated residue level (C_i). This would be appropriate if the degree of avoidance was a function only of concentration, i.e. if the avoidance response was purely of type (a) above.

However, for anticholinesterase compounds like methamidophos, the type (b) response is probably more important, with avoidance occurring mainly as a response to the onset of sublethal intoxication (physiological changes including inhibition of brain cholinesterase that are manifested externally as lethargy, loss of coordination etc.).

Equation (3) is inappropriate for representing this second type of avoidance response, because it implies that the avoidance of each food type is determined only by the concentration in that food type, whereas in reality it will be determined by the total dose including other food types.

It might be expected that if the threshold dose for the avoidance response is below the lethal dose, mortality will never occur from dietary exposure. In fact, mortality can occur because the avoidance response is not immediate (due to the time taken for absorption from the gut and transport within the body), so animals feeding rapidly may ingest a lethal dose before the onset of the response. This is the likely explanation for some documented field mortalities, including woodpigeons eating treated cereal seed (Hart *et al.*, 1999) and geese feeding on golf courses (Mineau *et al.*, 1994).

In those cases where sensory factors such as repellent taste or odour (type (a) response) have failed to prevent intoxication, mortality will only be avoided if sublethal intoxication causes cessation of feeding before a lethal dose is reached. In this situation (type (b) response),the factors determining the role of avoidance in preventing acute mortality include:

- The rate of ingestion,
- The rate of absorption and transport to target organs,
- The rate of metabolism and excretion,
- The internal dose threshold for cessation of feeding

- The extent and dose threshold of any regurgitation (which can play an important role in protecting some species but may be absent in others, Pascual *et al.* 1999a),
- The internal dose for lethality.

The critical role of ingestion rate has been demonstrated in extensive studies with feral pigeons feeding on wheat seed treated with the organophosphorous pesticide fonofos. These showed that the rate at which pigeons fed on fonofos-treated wheat seed was increased by prior food deprivation (increasing hunger), by acclimatising birds to restricted feeding times (2 or 4 hours per day), and by housing in groups (due to social facilitation or competition). Furthermore, mortality was absent when the birds were housed singly with unrestricted pre-test diet in these studies, but increased to 80% when all three of these conditions were combined (hunger, restricted feeding time and group housing; Hart *et al*., 1999). Video-recording showed that in some of the more severe conditions, the first bout of feeding on the test day was very rapid (averaging 37-65 pecks/minute) and very short (average 3-5 minutes), containing a high proportion of the normal daily food intake (Pascual *et al*., 1999b). Mortality depended on the dose ingested in this initial bout of feeding and on how much the bird subsequently regurgitated (Pascual *et al*., 1999a). There is limited information for other species: studies with untreated food have showed that the feeding rates of other species including pheasant (*Phasianus colchicus*), house sparrow and wood mouse can be significantly increased by experimental manipulation of feeding time, hunger and group size (Fryday *et al*., 2001; Hart, 2002).

These studies show that the rate at which captive animals feed, and consequently their ability to avoid consuming a lethal dose, is dependent on their motivational state and environmental conditions. The initial feeding rate of birds encountering contaminated food in the wild also can be expected to depend on many such factors, including:

- Hunger (depends on energy requirement, energy stores, etc),
- Energy content of food (affects amount needed),
- Competition and social facilitation when feeding in groups,
- Other motivational factors (e.g. need to reduce time exposed to predators, the need to share time with other behaviours such as drinking or watching for predators, diurnal rhythms which often include peak periods of feeding at dawn and dusk, and expectations regarding future food availability),
- Physical constraints (e.g. density of food items, time required for searching and handling, size of gizzard/crop/stomach and time required for clearance between "meals"),
- Attractiveness of food items (including any distasteful odour, taste or texture),
- Novelty/familiarity of food items (some species are more neophobic than others).

For longer term exposures, after the initial bout of feeding on contaminated food, additional factors become important, including:

- The ability of the animal to learn the association between illness and contaminated food,
- The availability of uncontaminated (or less contaminated) alternative foods, either at the same location or in other locations, ,
- Any factors inhibiting switching foods (e.g. food preferences, travel cost).

The many factors listed in the preceding paragraphs are complex and cannot be addressed simply by modifying the estimation of exposure. All of them may vary between species and between pesticides, and many are influenced by environmental conditions. Furthermore, the individual effects of these factors are not measured by current avoidance or toxicity studies, including those submitted for methamidophos. Therefore, any mechanistic model of the avoidance response would be highly speculative and uncertain. However, the studies submitted for methamidophos do provide information about the combined effect of these factors, by measuring the extent of the avoidance response for particular species under particular test conditions. The PPR Panel therefore tried to use the available studies to form judgements

about the potential influence of avoidance on risk for the proposed uses of methamidophos. However, when doing so it is essential to consider carefully how the many factors listed above affect extrapolation from laboratory studies to the species and conditions that are relevant in the field.

4.2 BIRDS

Evidence of avoidance in studies with birds and methamidophos

Relevant studies available to the PPR Panel are evaluated in Appendix 2. In summary, there are data on food avoidance associated with methamidophos for 3 species (mallard duck, bobwhite quail *Colinus virginianus* and Japanese quail *Coturnix coturnix japonica*), including some studies with very young birds and some with adult birds. The duration of the exposure period in these studies ranges from 1 – 15 days, and all show substantial reductions in food consumption. Mortalities occurred on day 1 only at high concentrations where a small part of the normal daily intake could contain a lethal dose. Starvation due to prolonged reduction of food intake was probably the main cause of the later mortalities. Results for two of the studies (Figures 7 and 9 in Appendix 2) suggest the existence of a threshold dose at about 20% and 50% of the LD50 respectively, above which further increases in dose are avoided by progressive reductions in consumption. In the study with young bobwhite quail (Figure 8) the avoidance threshold appears to be rather close to the lethal dose. However, these studies are likely to over-estimate the threshold dose for initiation of the avoidance response, as they measured consumption over 1-5 days during which period the birds may have stopped and resumed feeding several times. This bias is avoided if the threshold dose for avoidance can be estimated from the occurrence of reduced feeding in acute toxicity studies. In the case of methamidophos, reduced consumption was reported at ca. 20% of the LD50 in the acute study with bobwhite quail (Nelson, 1979a; summarised in Appendix 2). As this was the lowest dose tested, the true avoidance threshold for bobwhite quail may actually be lower than 20% of the LD50, but this cannot be determined without testing additional doses.

Extrapolation to yellow wagtail in field conditions

The key question for risk assessment is: how to extrapolate from these studies to the species and conditions that are relevant to the use of methamidophos in the field? Yellow wagtails are much smaller than the adult laboratory species, with different diet and behaviour. In all the laboratory studies, the subjects were acclimatised to a continuous and unlimited supply of a nutritionally complete diet, and the energetic requirement of the animals was reduced by the control of ambient temperature and limited opportunity for movement. In the field, there is wide variability in the availability of food, its energy content is often lower, there are greater energetic demands due to increased activity and variation in temperatures, and the time for feeding is restricted by the need for competing behaviours such as territorial defense and avoiding predators. As a consequence, it can be expected that yellow wagtails in the field need more food, but have less time to obtain it, so the rate of ingestion during feeding bouts may be much higher.

Conditions for captive and free-living animals differ in other ways that might also change the avoidance response. One of the most fundamental is that only treated food was available in the laboratory studies considered here, whereas alternative foods are normally available in the field. The notifier and RMS state that “A free living bird has always the opportunity to leave the field and to forage in uncontaminated areas”. This is true for most European landscapes (exceptions might occur in very intensively farmed areas, e.g. parts of eastern England, or in forest spraying). However, the existence of alternatives does not guarantee avoidance of a lethal dose, and becomes relevant only after the avoidance response is triggered. Several questions have to be asked: (a) in field conditions, will birds ingest a lethal dose before the

avoidance response is triggered? (b) once the avoidance response is triggered, what will surviving birds do – will they take the opportunity to leave the field, or switch to a different food within the field, or (after a delay) resume feeding on the same food? The answers to these questions depend partly on the interaction between PT, PD and AV, and are discussed in detail in section 5.

4.3 MAMMALS

The notifier submitted a one-day feeding study with laboratory mice, which is evaluated in detail in Appendix 2. The results showed strong avoidance starting between 50 and 158 mg a.s./kg diet, at a dose corresponding to 50-100% of the LD50 although, as for birds (above), this may represent repeated feeding bouts over the 24-hour period and therefore over-estimate the threshold dose for the initial avoidance response. The avoidance response was insufficient to prevent some mortality of wood mice at concentrations of 500 mg a.s./kg and above. In the field, a variety of factors discussed above (1.4.1) might increase feeding rate and consequently cause mortality of this species at lower concentrations. Again the avoidance response is likely to interact with PT and PD, and is discussed in the following section.

Food consumption was also measured in other mammalian studies submitted for methamidophos, including chronic feeding oncogenicity studies and 2-generation reproduction toxicity studies, conducted with both rats and mice at concentrations up to 58 ppm. There were reductions in body weight in all 4 studies but food consumption was reduced significantly only in 2. In a full assessment these studies might be helpful in assessing the role of avoidance in chronic, low-level exposures.

5 Influence of PT, PD and AV on exposure

5.1 INFLUENCE OF PT AND PD WITHOUT AVOIDANCE – BIRDS

As the factors affecting avoidance are so complex, the PPR Panel first examined the influence on exposure of PT and PD in the absence of avoidance by using equation (3) and setting AV_i to one (no avoidance). As PT and PD are both uncertain (see sections 2 and 3), exposure of yellow wagtails was calculated for different combinations of PT and PD and the results were used to plot Figure 1.

Exposure is shown in Figure 1 as diagonal lines. As expected, these increase with PT and also with increasing proportion of small insects in the diet (because they are assumed to contain higher residues than large insects, SANCO, 2002). For comparison, the acute oral LD50[27] of methamidophos for bobwhite quail is shown as a horizontal line. It can be seen that for a diet comprising 100% large insects, exposure does not reach the bobwhite LD50 even when PT=1, but that for a diet comprising 100% small insects this LD50 is exceeded when PT is greater than about 0.3.

For comparison with EU decision-making criteria it may be helpful to show the effect of PT and PD on the toxicity-exposure ratio (TER) and this is done in Figure 2. For the plausible worst case identified by the PPR Panel (PT = 0.5, Table 2; diet 100% small insects, Section 3.2), the acute TER is 0.6. This implies that the avoidance response may be critical in determining whether acute mortality occurs.

[27] The acute oral LD50 is normally used for assessing effects of acute exposures (SANCO, 2002).

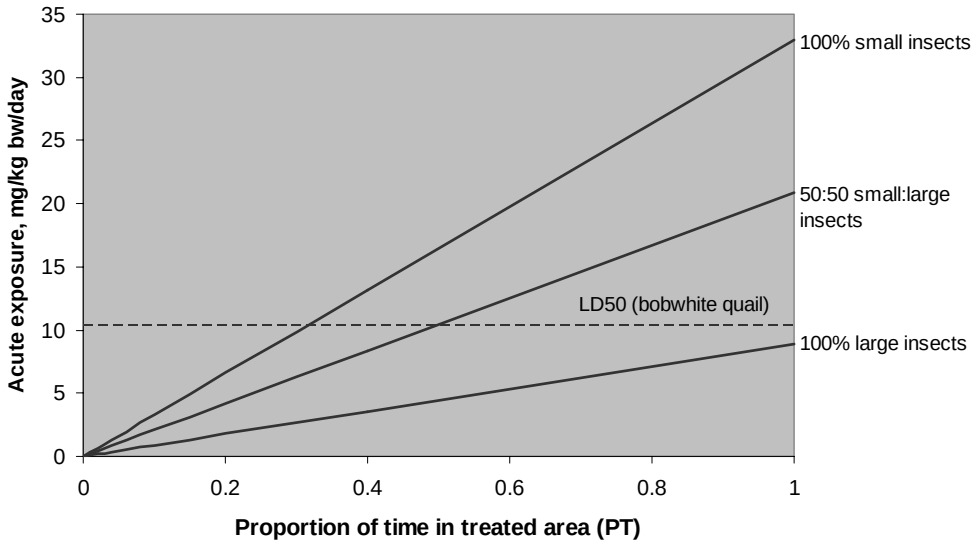

Figure 1. Relationship between the proportion of time spent in treated areas (PT), the proportions of diet comprising small and large insects (PD), and estimated acute exposure of yellow wagtail to methamidophos applied at 0.72 kg a.s./ha[28]. Avoidance is ignored in this graph (AV=1, see text for explanation). Other assumptions are the same as were used by the notifier and RMS and consistent with the EU Guidance Document (SANCO, 2002)[29].

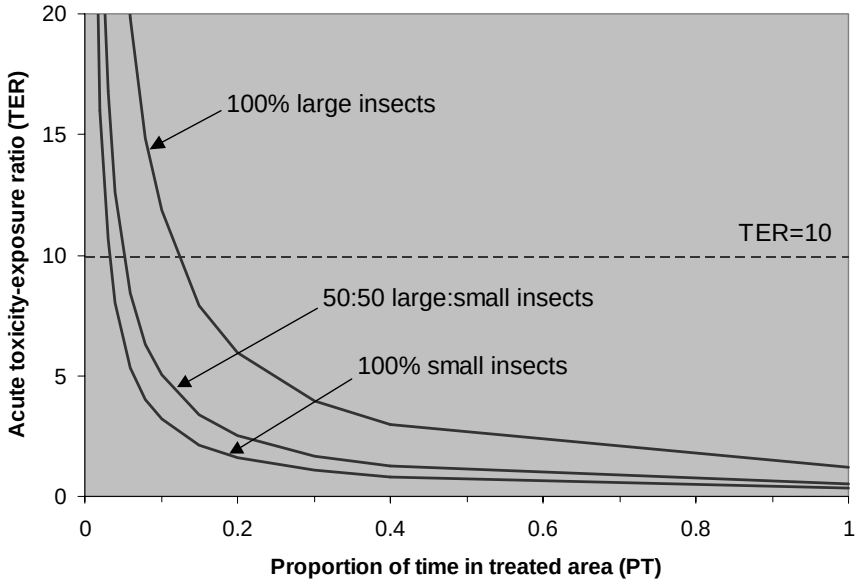

Figure 2. Relationship between the proportion of time spent in treated areas (PT), the proportions of diet comprising small and large insects (PD), and estimated acute TER (toxicity-exposure ratio) for yellow wagtail exposed to methamidophos applied at 0.72 kg a.s./ha. Avoidance is ignored in this graph (AV=1, see text for explanation). TER based on acute oral LD50 for bobwhite quail (10.54 mg a.s./kg). Other assumptions as in Figure 1.

[28] Rate for potatoes in northern EU in the EU DAR (Vol. 2), July 2004. The notifier has since proposed a rate of 0.48 kg a.s./ha for this use. This would reduce exposures in Fig. 1 by one third, and raise TER's in Fig. 2 by 50%.

[29] Body weight of yellow wagtail (*bw*) = 17 g, food intake rate (*FIR*) = 15 g/day, residue per unit dose (*RUD*) = 52 for small insects, 14 for large insects, multiple application factor (*MAF*) = 1, concentration (*C*) = 37 mg/kg for small insects, 10 mg/kg for large insects.

5.2 INFLUENCE OF AVOIDANCE – BIRDS

Assessment of the initial avoidance response

Results for two of the notifier's avian feeding studies suggest the existence of a threshold dose for the onset of the avoidance response, and mortalities occurred on day 1 only at high concentrations where a small part of the normal daily intake could contain a lethal dose (Section 4.2). This implies that risk depends critically on the birds' responses during their first bouts of feeding on the treated field after spraying. The key question is whether, in field conditions, yellow wagtails will ingest a lethal dose before the avoidance response is triggered? As mentioned earlier, the answer to this question depends crucially on the relationship between three factors: (i) the rate of methamidophos ingestion, (ii) the size of the difference between the dose thresholds for avoidance and lethality, and (iii) the latency (time delay) of the avoidance response after the avoidance threshold is reached. The PPR Panel considered these questions in turn.

Figure 3 shows what proportion of their daily food intake yellow wagtails require to reach different levels of exposure, and how this depends on the proportions of small and large insects taken. It can be seen that a yellow wagtail feeding entirely on small insects will obtain a dose equal to the LD50 for bobwhite quail in about 32% of its daily food intake.

However, toxicity varies between species and the LD50 for yellow wagtail could be either higher or lower than for the bobwhite quail. Detailed consideration of this issue is beyond the scope of this opinion, but an approximate indication of the possible range of LD50s is required for the discussion of avoidance. This can be provided by using selected points on the distribution of toxicity between species, such as the LD50 for the 5th percentile species or HD5 (hazardous dose for 5% of species). Methods for estimating the HD5 have been published by several authors, including Luttik & Aldenberg (1997) whose approach is cited in the EU Guidance Document (SANCO, 2002).

Using Luttik & Aldenberg's (1997) approach the median estimate of the avian HD5 for methamidophos is 1.85 mg a.s./kg[30] and this is shown as the lower horizontal dotted line in Figure 3. In the following assessment the PPR assumes that the LD50 of the yellow wagtail is actually equal to the HD5. In fact, there is a 95% chance that the true LD50 for yellow wagtail is above the HD5, and a 5% chance that it is lower. Using the HD5 therefore represents a conservative assumption, analogous (but not precisely equivalent) to the normal practice of comparing the acute avian toxicity-exposure ratio (TER) to a critical value of 10. Figure 3 shows that a yellow wagtail feeding entirely on small insects will obtain a dose equal to the HD5 in about 5.6% of its daily food intake.

The next step is to estimate the size of the gap between the threshold dose for avoidance and the lethal dose. In the acute toxicity study submitted by the notifier, reduced food consumption was recorded at about 20% of the lethal dose (Nelson, 1979a). However, the gap between avoidance and lethal thresholds may vary between species, and there is substantial uncertainty about it due to the small number of species tested.

[30] Calculated as the LD50 for bobwhite quail (10.54) divided by the extrapolation factor of 5.7 (Luttik & Aldenberg, 1997). Note we use the median estimate of the HD5 rather than the lower 95% confidence bound for the HD5 (which would be 0.3 mg a.s./kg).

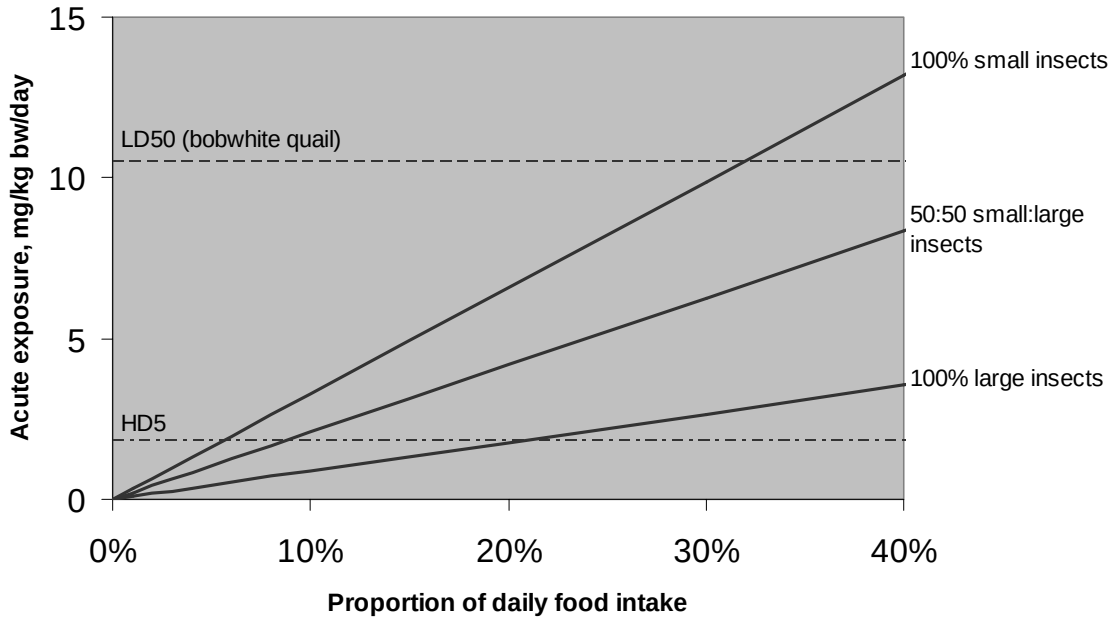

Figure 3. Estimated proportion of normal daily food intake required for yellow wagtails feeding in a field treated with methamidophos at 0.72 kg a.s./ha to reach different levels of exposure[31]. The three diagonal lines show results for different dietary compositions. HD5 is the median lethal dose (LD50) estimated for the 5th percentile species (see text for explanation). Other assumptions as in Figure 1[32]. See text for use of this diagram to assess initial avoidance response.

If it is assumed that the LD50 for the yellow wagtail is equal to the HD5 (1.85 mg a.s./kg) and avoidance threshold is 20% of this, then Figure 3 shows that the gap between them corresponds to about 4.5% of the daily food intake of yellow wagtails (when feeding entirely on small insects).

The next step is to estimate the time taken for a yellow wagtail to find and consume 4.5% of its daily intake. Davies (1977) found that yellow wagtails at Oxford UK consumed 9 insects per minute (mostly 3-10 mm) when feeding singly at dung pats, but 29-36 insects per minute (mostly 2-3 mm) when feeding in flocks at pools. However, the intakes were reversed and more similar when expressed in terms of energy: 285 J/min and 196 J/min respectively. At these rates of intake, the yellow wagtail would take between 12 and 17 minutes to obtain 4% of its daily food requirement (based on the daily energy requirement of 74kJ assumed by the notifier and RMS and derived from the EU Guidance Document (SANCO, 2002).

The final step is to assess whether this time (12-17 minutes) exceeds the time taken between ingestion of the avoidance threshold dose and cessation of feeding. The most detailed information available to the PPR Panel on the timing of effects after exposure to methamidophos is from an acute oral toxicity study with adult dark-eyed juncos (*Junco hyemalis*), in which "signs including fluffed feathers, depression, dyspnoea, ataxia, tremors,

[31] Note the estimates relate to the ingested dose. Similar graphs for internal doses might be non-linear due to limitations in absorption when concentrations in the gut are high.

[32] Note that these results are calculated using equation (3) in exactly the same way as Figure 7, but that the horizontal axis is labeled as "proportion of daily food intake" rather than PT. This is because the focus here is on a single bout of feeding on the treated field (expressed as a percentage of the normal daily food intake) rather than on the proportion of food obtained on the field over a whole day (which is the usual interpretation of PT).

falling and convulsions were seen 10 minutes after dosing" (Zinkl *et al.*, 1981, cited in Draft Assessment Report (DAR) for methamidophos, Vol. 3 Annex B9). [33]

These calculations imply that the time taken, for yellow wagtails to ingest a dose equivalent to the gap between the avoidance and lethal thresholds (12-17 mins), could plausibly be in the same order as the time taken between ingestion of the avoidance threshold dose and cessation of feeding (10 min). If the former time were actually shorter than the latter, then a lethal dose would be ingested before cessation of feeding and, unless part were regurgitated (e.g. Pascual *et al.*, 1999a), result in mortality. If the former time were actually longer than the latter, then feeding would cease before a lethal dose was ingested. Because the PPR Panel's estimates of these times are rather similar, and are based on many uncertain assumptions, it is uncertain which outcome should be expected.

The assessment above considers only avoidance responses arising through sublethal intoxication following ingestion of food contaminated with methamidophos. Other mechanisms may contribute to the avoidance response in the notifier's studies but their contributions are uncertain. Fields sprayed with some organophosphorous compounds smell strongly unpleasant to humans. It is uncertain to what extent birds and wild mammals share this sensation. Odour-based behaviour varies widely in birds and tends to be more developed in species with large olfactory organs (e.g. some seabirds and predatory birds), but in fact sensitivity to smell varies (Bang & Wenzel, 1985). Pigeons avoided food treated with the organophosphorus insecticide fonofos more strongly when presented in bowls than on trays, a difference that was attributed to vapour effects (Fryday *et al.* 1998) but smell did not prevent the same species ingesting lethal doses in conditions promoting fast feeding (Hart *et al.*, 1999). Furthermore, it is clear that neither smell nor taste is sufficient to completely deter birds from feeding in methamidophos-treated fields, as measurable residues of methamidophos have been found in the guts of sage grouse (*Centrocercus urophasianus*, Blus *et al.*, 1989) and ring-necked pheasants (Grove *et al.*, 1998) collected in and around potato fields sprayed at 1.12 kg methamidophos/ha. Finally, birds such as yellow wagtails that have young in the field are unlikely to desert them for long unless debilitated.

Uncertainties affecting the assessment in this section include:

- uncertainties affecting the calculations in Figure 3, most importantly the concentrations expected on small insects (see SANCO 2002, p. 11),
- uncertainties concerning the rate of absorption of methamidophos from the gut,
- uncertainty about possible differences between the LD50 from acute oral dosing versus dietary exposure over timescales relevant to this assessment,
- uncertainty concerning possible differences between responses to active substance and formulation (may affect LD50, time to effects, avoidance),
- uncertainty concerning extrapolation of the LD50 from test species to the yellow wagtail,
- uncertainty concerning the avoidance threshold for yellow wagtail as a proportion of its LD50,
- extrapolation of energy ingestion rates from yellow wagtails feeding at pools and dung pats (Davies 1977) to the conditions immediately post-spraying in crops supported for methamidophos,
- uncertainty in the estimation of daily energy requirement of yellow wagtails from a general equation based on body weight (SANCO 2002),
- uncertainty concerning the relationship between the timing of signs seen in the acute toxicity test with juncos and the timing of the avoidance response in yellow wagtails,

[33] It should be borne in mind that absorption of the active substance into the tissues following administration of an acute oral dose may be more rapid than would occur during dietary ingestion of contaminated insects, so the time to effects might be longer for a dietary exposure.

- uncertainty concerning the contribution to avoidance of sensory responses to methamidophos (smell, taste).

The assumptions made by the PPR Panel for most of these uncertain elements are intended to be unbiased, i.e. higher or lower values are roughly equally likely. An important exception is the LD50, where in keeping with the approach described by SANCO (2002, p. 23) we use the HD5: there is a 5% chance (approximately) that the true LD50 is lower, and conversely a 95% chance that the true LD50 is higher. Higher values (HD10, HD50 etc) could be chosen, depending on the degree of conservatism desired. As the LD50 increases, the absolute size of the gap between avoidance threshold and LD50 may increase, which would increase the chance that feeding stops before a lethal dose is ingested.

In summary, extrapolation of the avoidance response from tested to untested species, and assessment of its influence on the risk of mortality in field conditions, is highly uncertain. However, if it is desired to apply a similar degree of conservatism regarding between-species variation in toxicity as that described in the EU Guidance Document (SANCO, 2002), then it is plausible that yellow wagtails might feed fast enough to reach a lethal dose before manifestation of the avoidance response. Options for further studies that might reduce the uncertainty of this conclusion are outlined in section 7.

For a full assessment, similar considerations could be developed for other bird species with potentially significant exposures. Based on earlier sections, the skylark might be a strong candidate for this.

The PPR Panel's assessment of the initial avoidance response contrasts markedly with that of the notifier and RMS. After reviewing the studies by Barfknecht (2001) and Stromborg (1986) (see Figure 6 in Appendix 2) they conclude that "this strong avoidance reaction will prevent a bird from the ingestion of lethal amounts of methamidophos-residues".

The notifier and RMS give 3 reasons to support their conclusion:

1. A free-living bird has always the opportunity to leave the field and to forage in uncontaminated areas.
2. Especially during the summer months and in southern European regions no severe pressure (like cold weather with snow) will force a bird to ingest higher amounts of unpalatable food items.
3. Also the residues per single food item (e.g. one insect, seed or leaf) are not that high that a severe intoxication may occur after the ingestion of a few items (as it may occur with treated seeds or granular formulations).

The first of these arguments has no relevance to the initial avoidance response (cessation of feeding) discussed in this section, because it applies only to the choices of the bird after the avoidance response is initiated (see next section). The second argument, as stated, is also relevant only to food perceived by the bird as unpalatable, i.e. after the threshold for the avoidance response has been exceeded. In any case, the PPR Panel's assessment is based on feeding rates from studies in the UK in May and not on extreme conditions such as those mentioned by the notifier and RMS. Regarding the third argument, although the dose per ingested item does tend to be higher for seeds or granular formulations, the outcome of the PPR Panel's assessment demonstrates that it may also be possible for birds feeding on insects to obtain lethal doses quickly enough to overcome the avoidance response.

Finally, the notifier and RMS both argue that "A risk assessment dealing with this circumstance cannot be performed in order to achieve a TER-factor of 10, because the avoidance reaction is linked to the sensitivity of the exposed species: in a more sensitive species the pesticide-induced anorexia will turn up at lower concentrations than in a less sensitive species. Therefore

a safety factor for differences in species sensitivity is inappropriate to be incorporated into the TER-figure." This is unlikely to be correct, because for more sensitive species the absolute difference in dose between the 2 thresholds is likely to be smaller[34], and hence more susceptible to be overtaken when the rate of dose ingestion is high. Therefore variation in species sensitivity should still be taken into account, although, as the PPR Panel's assessment illustrates, in a way that is different from the standard TER approach (indeed the PPR Panel's approach based on Figure 3 does not involve calculating a TER).

Assessment of avoidance over longer timescales

After initiation of an avoidance response, the key question is what the birds that survive the initial exposure will do – will they take the opportunity to leave the treated field, or switch to a different food within the field, or (after a delay) resume feeding on the same food?

After the onset of avoidance and other sublethal effects, birds such as yellow wagtails that are resident or nesting in the field may rest in the field waiting to recover, rather than leaving it. If they do leave the field, they are likely to return later, especially if they have eggs or nestlings. The question then is whether they will resume feeding in the field, or only visit the field and feed elsewhere. One possibility is that they may sample food from the field periodically, as occurs daily for captive birds in dietary toxicity studies (e.g. Figure 9 in Appendix 2). In this case the animals would suffer a series of sublethal exposures. These exposures might be expected to decrease in severity if the birds learned to recognise the presence of the toxicant more rapidly on successive occasions, or if the concentration of the toxicant declined with time. The role of these various factors in determining the pattern of longer-term exposure would be difficult to assess with any certainty. In one LC50 study the survivors appeared to resume feeding within a few hours when presented with clean food (Nelson, 1979b), but this does not tell us how rapidly they would recognise the presence of methamidophos if exposed again subsequently.

5.3 INFLUENCE OF PT AND PD WITHOUT AVOIDANCE – MAMMALS

The PPR Panel applied the same approaches more briefly to assess the influence of PT and PD on exposure and risk for the wood mouse (Figure 4). The results show that, for the diet assumed by the notifier and RMS (30:70 seeds:large insects), methamidophos applied at 0.72 kg a.s./ha gives a TER of 13. Diets of 100% large insects and of 100% seeds also give TERs mainly above 10. The notifier and RMS used several assumptions (included in Figure 4) that reduce the TER: they assumed no consumption of vegetative plant material, they used a residue per unit dose of 52 for seeds (rather than 87 as implied in the recommendations section of Annex 2 in the EU Guidance Document; SANCO, 2002), and they used a multiple application factor (MAF) of 1 for seeds (the EU Guidance Document gives no guidance on this, specifying only that a factor of 1.5 should be used for short grass and leafy material), and they used an LD50 for mice estimated from the one-day feeding study rather than the standard acute LD50. The appropriateness of these assumptions for the standard TER assessment in this case is outside the specific scope of the question to the PPR Panel, with the exception of the assumption regarding the consumption of plant material.

As vegetative plant tissue is often present in wood mouse diets (see section 3) and the residues and daily intake of leafy material can be much higher than other foods, the PPR Panel decided to assess a realistic diet including this. As mentioned in section 3, the diet reported by Pelz (1989) for wood mice in Rhineland arable farms included 25% dicot seeds, 25% insect larvae

[34] If the gap between the thresholds were a fixed absolute amount, then the avoidance dose would be negative for very sensitive species, which is impossible. It is more likely that the gap between the thresholds is positively correlated with them both, although probably not a fixed proportion.

(assumed here to be "large" insects"), and 9% vegetative plant matter. When this diet is assessed including the standard assumptions for leafy material (SANCO, 2002) together with the notifier's assumptions for other foods, but with no avoidance, the TER is below 10 for values of PT above about 0.6 (which are expected for wood mice, see section 2). This suggests that in the absence of avoidance, there would be a potentially significant risk to wood mice in some circumstances. The PPR Panel therefore considers the influence of avoidance for wood mouse in the following section.

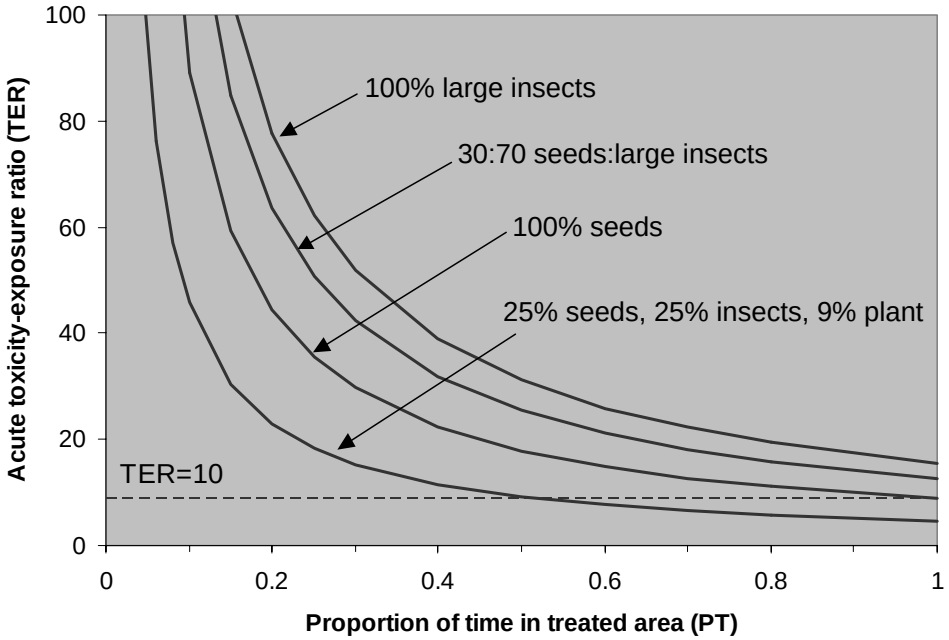

Figure 4. Relationship between the proportion of time spent in treated areas (PT), the proportions of diet comprising seeds and large insects (PD), and acute TER (toxicity-exposure ratio) estimated for wood mice exposed to methamidophos applied at 0.72 kg a.s./ha. Avoidance is ignored in this graph (AV=1, see text for explanation). Other assumptions are the same as were used by the RMS[35]. TER based on LD50 for mouse derived from 1-day feeding study (79.95 mg a.s./kg) as in refined assessment by notifier and RMS.

5.4 INFLUENCE OF AVOIDANCE – MAMMALS

The PPR Panel briefly considered the influence of avoidance on risk to wood mice, using the same approach as was developed for birds. The proportion of daily food intake required to reach different levels of exposure for wood mice consuming different foods is shown in Figure 5. As the focus is on the first bout of feeding after spray application, prior to the initiation of the avoidance response, it is assumed that only one type of food is taken and that this can be either large insects, small seeds or leafy plant material. Assumptions regarding residues in these foods are as for Figure 4.

[35] Body weight of wood mouse (*bw*) = 20 g; food intake rate (*FIR*) = 34 g/day if consuming only non-grass herbs, 4.8 g/day if only seeds, 10.2 g/day if only large insects; residue per unit dose (*RUD*) = 52 for seeds, 14 for large insects, 87 for herbs, multiple application factor (*MAF*) = 1.6 for herbs, 1 for seeds and insects, concentration (*C*) = 37 mg/kg for seeds, 10 mg/kg for large insects, 100 mg/kg for herbs. These assumptions are consistent with the EU guidance document except the *MAF* for seeds (normally 1.6) and the *RUD* for seeds, which page II-8 indicates should be the same as for herbs (87) (SANCO, 2002). However, *MAF* and *RUD* were not the focus of the question to the PPR Panel, so the RMS assumptions are used here.

The exposures are compared with acute LD50s rather than the LD50 from the one-day feeding study, since here the focus is on acute exposure during the first bout of feeding. Luttik and Aldenberg (1997) quote a median HD5 of 12.4 mg a.s./kg estimated from LD50s for 6 mammal species (range 10-32 mg a.s./kg), and this is shown together with the acute oral LD50 for rat reported by the notifier (9.1 mg a.s./kg), which in this case happens to be lower than the HD5. The results in Figure 5 show that a wood mouse is unlikely to achieve the HD5 rapidly when feeding on insects or seeds, implying that there should be plenty of time for the avoidance response to prevent ingestion of a lethal dose. However, a wood mouse feeding on leafy material could obtain a lethal dose within 8% of its daily intake, if the LD50 for this species were close to the HD5. The position of the dose threshold for avoidance cannot be estimated with any precision from the one day dietary study (Figure 11 in Appendix 2), as the animals may have stopped and resumed feeding several times within the day. If it is assumed that the avoidance threshold for methamidophos in wood mice is about 20% of the lethal dose (as assumed for the yellow wagtail), then the gap between this and the lethal dose corresponds to about 6% of the daily food requirement when feeding on leafy material. Wood mice are predominantly nocturnal so presumably obtain most of their daily food within a period of about 8 hours, so the time taken to ingest 6% of their daily intake might be in the order of 30 minutes[36]. This is longer than the corresponding time estimated for yellow wagtail (12-17 minutes), so if the latency of the avoidance response is similar in the two species then the risk will be lower for wood mouse.

This assessment is even more uncertain than that for birds, because fewer short-term feeding studies were available for mammals and no data were provided to the PPR Panel regarding the feeding rate of wood mice in the field, nor the timing of effects in mammals. Based on the available information, the PPR Panel cannot exclude the possibility that wood mice feeding on leafy material immediately after methamidophos application might ingest a lethal dose before onset of the avoidance response, although the risk for wood mouse seems somewhat lower than for yellow wagtail.

[36] The PPR Panel did not find any information on short-term feeding rates of wood mice in the wild, but in laboratory studies with varying time periods of food deprivation this species was shown to consume 7-32% of its normal daily food intake within 2 hours (Hart, 2002).

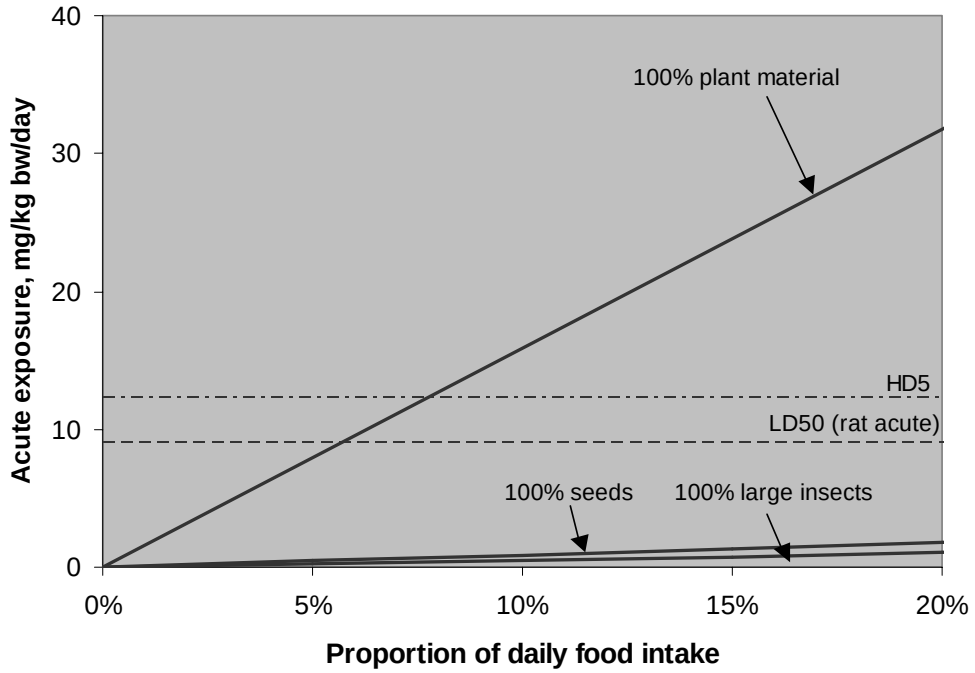

Figure 5. Estimated proportion of normal daily food intake required for wood mice feeding in a field treated with methamidophos at 0.72 kg a.s./ha to reach different levels of exposure. The three diagonal lines show results for different dietary compositions. HD5 is the median lethal dose (LD50) estimated for the 5th percentile species, LD50 is from acute oral rat study (see text for explanation). Other assumptions as in Figure 4. See text for use of this diagram to assess initial avoidance response.

6 Additional considerations

6.1 OTHER SPECIES

The notifier's field studies in Germany and Italy support their choice of yellow wagtail as a species with potentially high exposure. Their data together with other published studies suggest that skylarks also deserve attention. The potential for exposure of herbivorous species with larger foraging ranges such as woodpigeon is less clear, because the notifier's studies were less well suited to quantify their use of supported crops. A full assessment should consider them further, especially because their food is likely to contain higher residues than that of wagtails and skylarks.

The notifier's field studies confirm the potential for exposure of wood mouse but provide much less information for other mammals. Shrews also deserve attention as their small size, high metabolic rate and insectivorous diet could make them more exposed than wood mice. A full assessment should also use information from the general literature to consider the exposure of larger mammals.

6.2 OTHER TIMESCALES

The PPR Panel's assessment has focussed mainly on the initial acute exposure, although it also considered briefly the role of avoidance in longer-term exposures for birds (section 5.2). Similar considerations would be appropriate for mammals. As part of their justification for not conducting a long-term assessment for mammals, the notifier and RMS argue that food

avoidance will limit exposure, but this is unlikely to operate strongly at concentrations relevant to longer-term exposures.

6.3 OTHER ROUTES OF EXPOSURE

The PPR Panel assessment has focused entirely on dietary exposure of adult birds and mammals. A comprehensive assessment should consider the potential significance of other routes of exposure, including:

- exposure via drinking,
- dermal exposure,
- dietary exposure of young birds and mammals,
- overspray of eggs and nestlings[37].

The notifier and RMS state that "some further implications will be made for the exposure of drinking water" but do not report any assessment for it. Given the high toxicity of methamidophos, a small bird (20g) might reach a TER of 10 by drinking 0.01 ml of spray solution[38] from leaf whorls, or if it formed temporary puddles on the soil surface. The potential importance of this route is emphasised by a report of an incident in Germany in which the deaths of over 100 house sparrows, linnets and greenfinches were attributed to poisoning due to drinking from leaf whorls after application of methamidophos at 0.36 kg a.s./ha (Hommes *et al.*, 1990). The same authors reported similar incidents for methomyl, oxydemeton-methyl, mevinphos and dimethoate, and a further incident involving methamidophos was reported subsequently[39].

A recent review has derived general regression relationships predicting the occurrence of avian mortality in field studies and poisoning incidents (Mineau, 2002). The results suggest that both acute and dermal toxicity contribute significantly to avian mortality. The database used for the review is available on the journal publisher's website and includes 4 cases of methamidophos used in cole crops and potatoes, all of which included evidence of avian mortality[40]. Furthermore, the regression relationship predicts mortality in 10% of fields treated with methamidophos at rates around 0.1-0.2 kg a.s./ha, and in 50% of fields treated at around 0.5-0.8 kg a.s./ha (Table 5 in Mineau, 2002). However, this regression relationship is based largely on North American field data. The PPR Panel recommends that the applicability of these results to European conditions should be considered.

6.4 SUBLETHAL AND REPRODUCTIVE EFFECTS

Even if feeding rates are sufficiently slow for avoidance responses to prevent birds and mammals reaching lethal doses, they will still over-run the avoidance threshold to some extent and presumably suffer some degree of sublethal intoxication. Furthermore, this might happen on repeated occasions if animals later resumed feeding on the same field (as discussed for birds in section 5.2).

[37] Based on potatoes treated at 0.72 kg a.s./ha: an area of 1.4 cm^2 could contain sufficient dose for a 10 g nestling to reach a TER of 10.

[38] Based on potatoes: 0.72 kg a.s./ha in 400 l/ha.

[39] Reports for 1998-2003, http://www.bvl.bund.de/pflanzenschutz/Monitoring.htm

[40] One incident involving over 100 songbirds attributed to birds drinking from leaf whorls after ground spray application to cole crops at 0.36 kg a.s./ha (Hommes et al. 1990); a set of incidents in cabbages involving large mortality of starlings and some of other species, with detected residues of methamidophos and acetylcholinesterase (AChE) inhibition up to 76% (US EPA, Undated); one incident of 2 dead juvenile pheasants with >90% AChE inhibition and intestinal residues of methamidophos (Grove *et al.*, 1998); mortality and intoxication of Sage grouse in potatoes (up to 65% AChE inhibition, intestinal residues of methamidophos; Blus *et al.*, 1989). Applications to potatoes assumed by study authors to be aerial sprays at 1.12 kg a.s./ha.

The potential consequences of this should be considered, especially the possibility that single or repeated sublethal effects (e.g. lethargy, ataxia) in parent animals could increase the risk of predation, or impair the feeding and survival of young.

6.5 ASSESSMENT FOR WIDER POPULATIONS

This opinion has focussed primarily on assessing exposure for local populations, on and around fields treated with methamidophos. The assessment in section 5 suggests that for methamidophos, the primary determinant of acute risk is exposure during the first bout of feeding on the field after spraying. Even if an animal spends little time on the field overall (PT low), the risk may be high if it visits to feed shortly after spraying. In this situation, therefore, the primary importance of PT is in determining, together with the frequency of applications, what proportion of individuals will feed in the field during the critical period. Section 2.1 considered this for the case of yellow wagtail, and suggested that, as a rough approximation, in areas similar to the region of Germany used for the notifier's field study, approximately one third of the fields may be potatoes and, if all fields were treated with methamidophos, then approximately one third of the yellow wagtails might be exposed. This exposed part of the population might or might not experience significant mortality, depending on the true values of the factors considered in section 5.2. Thus, in major potato-growing areas, acute mortality of yellow-wagtails due to methamidophos might be estimated (very approximately) as falling somewhere between 0 and 30%, if all potatoes were treated with methamidophos. Similar estimates could be developed for other species and other endpoints (e.g. reproductive effects) but, on the available data, they will be similarly uncertain.

Mason & Macdonald (2000) suggest that eggs and young of yellow wagtails still present in UK potato fields in June and July are unlikely to survive harvesting of the potatoes. However, the PPR Panel considers that some yellow wagtail young present in potato crops at the time of methamidophos application might be old enough to fledge before harvest. Therefore the relative timing of breeding, fledging and harvest in supported crops should be considered more closely if a full assessment of the population consequences of effects on nestlings is required.

7 Options for reducing uncertainty

The PPR Panel assessment has identified major uncertainties affecting all three of the factors considered (PT, PD and AV) and also in other areas (e.g. section 6). The PPR Panel briefly reviewed the types of study that could be considered if it were decided that more certainty is required.

The assessment of PT (time spent or diet obtained in treated areas) for yellow wagtails could be refined by use of radio-tracking. If done, this should include assessment of changes in field use immediately following the application of insecticides, as this could have a critical effect on exposure. In designing such a study, careful attention should be paid to the difficulties discussed above in section 2.

The assessment of dietary composition (PD) for both yellow wagtails and wood mice could be refined, although it is strongly preferable that this should be done without killing animals (e.g. by faecal analysis). Pooling of samples should be avoided, to provide information on variation in diets between individuals and over time. Again, it would be desirable to focus such studies on the period immediately following insecticide application as this is critical for exposure.

Several options exist for refining the assessment of avoidance (AV), but none of them are simple.

- Experimental studies could be conducted to characterise more precisely the various factors determining the avoidance response (e.g. the levels of the avoidance and lethal thresholds, the time between ingestion of the avoidance dose and manifestation of the avoidance

response, and the factors affecting feeding rate). This approach has the advantage that it should improve understanding of the underlying mechanisms, but it would require extensive, novel animal studies. Furthermore, all these factors are likely to vary between species and conditions, so extrapolations between species and conditions would remain very uncertain until a substantial body of data was accumulated.

- To avoid the need to quantify detailed mechanisms, and to avoid the need to extrapolate between species and conditions, the effectiveness of the avoidance response could be tested in experiments with the relevant species under realistic worst-case conditions, in captivity. If the avoidance response were effective under these conditions it could be assumed to be effective for that species in all other circumstances. Disadvantages of this approach are that it requires captive testing of wild species which may raise ethical and legal issues, and that it may be difficult to define "realistic worst-case conditions" with sufficient certainty (because it requires at least a partial understanding of the underlying mechanisms). More complex tests involving realistic availability of untreated feeding choices[41] would be required to assess avoidance in longer-term exposures. Of the species considered in this assessment, the wood mouse is probably most amenable to such studies (e.g. Hart, 2002). Experiments with surrogate species could be considered, but reintroduce the uncertainties of extrapolating to the species at risk.
- Efforts could be made to confirm the operation of the avoidance response in the field either by measuring avoidance directly (e.g. McKay *et al*., 1999) or by monitoring sublethal and lethal effects. Both types of study suffer from low power due to natural variability in animal behaviour, the difficulty of detecting mortalities (unless radio-tracking is used) and the difficulty of recovering casualties and confirming the cause of death. Furthermore, it may be necessary to repeat the study for a substantial number of species, sites and occasions to represent the range of relevant species and conditions, and to quantify the frequency of impacts with adequate certainty.

If avoidance responses really are as effective as the notifier and RMS suggested, then it might be possible to demonstrate this in a small number of well-designed feeding experiments with relevant species in worst-case conditions. However, if these studies showed the response to be only partially effective, more demanding studies might be required to characterise the expected frequency of impacts. It would be desirable in any such studies to collect detailed information on consumption and the timing of effects to some understanding of the mechanisms involved. Such data are best obtained by video recording to avoid disturbance during the critical early feeding bouts.

It is difficult to predict which of the above options would be most efficient in reducing uncertainty. Avoidance studies can be expensive, especially when conducted with non-standard species, and involve substantial ethical considerations. Field studies involving radio-tracking are very expensive, especially if multiple sites are required to ensure representativeness and if the study has to be organised to focus on a short period after insecticide application. On the other hand, improved data on PT and PD would have additional benefits if they were relevant to the assessment of other pesticides as well as methamidophos.

Consideration could also be given to refining other aspects of the assessment, e.g. residue levels on relevant food items, if the notifier or RMS believed these might differ significantly from the levels they have assumed up to now.

In addition, the PPR Panel suggests that consideration be given to investigating risk from exposure via drinking water, dermal exposure of adults and overspray of nestlings, as it appears from preliminary considerations and incident reports (section 6) that these might be more significant than the dietary route.

[41] Simultaneous provision of treated and untreated foods side by side may be unrealistic for many field scenarios.

CONCLUSIONS AND RECOMMENDATIONS

The PPR Panel concentrated its assessment on the use of methamidophos on potatoes in northern EU Member States in summer as an example[42]. Other uses of methamidophos should be assessed using comparable approaches, which could also be applied to other substances.

The PPR Panel concentrated its assessment on two species considered by the notifier and RMS, the yellow wagtail and wood mouse, as they make substantial use of the crops supported for methamidophos. However, the PPR Panel considers that some other species including skylarks and shrews may also make substantial use of the crops supported for methamidophos, and may therefore deserve further attention in the risk assessment. Further species may require consideration when assessing uses of methamidophos on crops in arid areas of the Mediterranean region.

The PPR Panel agrees with the assessment of the notifier and RMS that local populations of wood mice may obtain all of their food from treated fields (PT=1), based on evidence from radio-tracking studies. The PPR Panel does not agree with the RMS and notifier's assessment that yellow wagtails would obtain only 5% of their food from treated fields after spraying. A detailed review of field observations indicates that yellow wagtails may nest in potato fields and that some individuals may obtain close to 100% of their food within the field. The PPR Panel agrees with the notifier and RMS that use of the field is likely to decrease after insecticide application due to reduced availability of insects, but the potential for exposure immediately after spraying remains because yellow wagtails are known to feed opportunistically on local concentrations of dead insects under some circumstances.

The estimates used by the notifier and RMS for dietary composition (PD) for yellow wagtail and wood mouse represent averages between individuals and over time. The PPR Panel notes that this will under-estimate acute exposure of individual animals. Yellow wagtails will take either small or large insects, and are known to feed opportunistically on local concentrations of small insects such as aphids under some circumstances. It is therefore plausible, that some yellow wagtails would feed exclusively on small insects after methamidophos applications. Wood mice have wide-ranging diets including seeds, insects and plant foliage, but field data show that during short periods an individual wood mouse may concentrate its feeding on any one of these foods.

In laboratory studies, two quail species, mallard and the laboratory mouse showed strong avoidance (reduced consumption) of food treated with methamidophos. The notifier and RMS assume that these results can be extrapolated without adjustment to yellow wagtails and wood mice in the field, but the PPR Panel has identified some important factors that could influence the degree of avoidance in the field.

The PPR Panel used a graphical approach to explore the influence of these factors on the exposure of yellow wagtails and wood mice to methamidophos. In the course of these considerations it became apparent that current guidance on how to incorporate avoidance in the estimation of bird and mammal exposure is inappropriate if the avoidance response operates at a threshold dose, as is likely for methamidophos. The PPR Panel developed an alternative approach for assessing the potential role of avoidance. The mechanisms involved are complex and depend upon whether the animal feeds quickly enough to ingest a lethal dose before the avoidance response is manifested. These factors are poorly quantified by currently available data. To assess them, the PPR Panel had to make a number of uncertain

[42] The PPR Panel selected this use of methamidophos as an example, for reasons explained in section 1.2. Risks for other uses may be different, depending on application rates and other factors.

assumptions (for details see section 5.2). These assumptions were intended to be realistic rather than conservative, with the exception of the conservative assumption that each species is at the 5th percentile of the species sensitivity distribution (HD5), which is consistent with an approach described by SANCO (2002, p. 23). On the basis of these assumptions, it appears possible that both yellow wagtail and wood mouse might feed quickly enough for mortality to occur in field conditions. The PPR Panel identified several options for laboratory or field studies to assess these risks with more certainty.

The PPR Panel briefly considered some other routes of exposure to methamidophos (drinking, dermal exposure, overspray of nestling birds), which were not assessed by the notifier and RMS. Preliminary consideration suggests that, for methamidophos, the risk from these routes may be higher than the risk from dietary exposure.

DOCUMENTATION PROVIDED TO EFSA

1. Letter from Mr A. Checchi-Lang from the Health & Consumer Protection Directorate-General requesting a consultation EFSA on methamidophos, with ref. E1/DVB D/510472(04), 22 April 2004.
2. SANCO, 2002. Guidance document on Risk Assessment for Birds and Mammals under Council Directive 91414EEC (Doc SANCO/4145/2000 final, 25 September 2002).
3. Draft Assessment Report (DAR) for methamidophos, Vol 1, level 1 to 4, p 1-89.
4. Draft Assessment Report (DAR) for methamidophos, Vol. 3 Annex B9 Ecotoxicology, p1-51.
5. Addendum 1 DAR for methamidophos, Vol. 1, level 2,3 and 4, undated, page 1-55.
6. Addendum 1 DAR for methamidophos, Vol 3, Annex B, undated, page 2-86.
7. Addendum 2 DAR for methamidophos, Vol 1, level 2 and 3, July 2003, page 1-38.
8. Addendum 2 DAR for methamidophos, Vol 3 Annex B, July 2003, page 1-89.
9. Comment by Danish authority (EPA) on Evaluation WG meeting 17-18 Sept. 03, ref ABA/STM/11, 26 April 2004.
10. Comment by UK authority (PSD) ref. ASY 58, 16 October 2003.
11. Comment by NL authority following Evaluation WG meeting (17-18 September 2003), 6 October 2003.
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24. List of supported uses supported by available data (11 Feb. 2003), 1.

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APPENDIX 1 - DETAILED EVALUATION OF FIELD STUDIES PROVIDED BY THE NOTIFIER

The notifier submitted reports on two field studies that aimed to evaluate which mammals and birds occur in potato and tomato fields and which of them are herbivorous (Barfknecht, 2003a, b). The notifier intended them to be "generic" studies, providing information relevant to a range of pesticides used on potatoes in "Middle European" areas, and on tomatoes in "southern European" areas. The methodology of the two studies was essentially the same, with minor differences noted below.

Tomatoes are not a supported use of methamidophos. Therefore the relevance of the tomato study to methamidophos is limited to assisting general considerations about the extrapolation of PT between crops and between different climatic regions.

Study sites

The studies were focussed on 4 potato fields (2.5–10.4 ha) in the vicinity of Rommerskirchen (Nordrhein-Westfalen, Germany), and 4 tomato fields (3.7 – 7 ha) in the vicinity of Codogno (Lombardia, Italy).

The tomato sites were in a northern part of Italy where the climate is not representative of the wider Mediterranean region due to the climatic influence of the Alps and the vicinity to water bodies and forest areas. In particular, in more southerly sites irrigation, which is common in these crops, can be the only source of water during long periods, whereas rainfall was reported during 25% of the days in the notifier's study. The study report cites "general growing procedure" for tomatoes in the study region as including 30 to 35 mm irrigation every 13 days, but irrigation is not mentioned in the description of procedures for the study sites. Spanish locations with Mediterranean climate have many fewer days with rainfall during the studied months, and close to zero in some places (INM, 2001). In these circumstances non-crop vegetation attractive to non-target vertebrates can be more abundant in the irrigated field than in off-field areas. Therefore, in regions that are more dependent on irrigation, wildlife may make more use of the cropping area than is indicated by notifier's study.

The overall density of birds in the fields in the tomato study (0.82 birds/ha) was similar to data from other Mediterranean habitats with small/medium height vegetation (about 1 bird/ha, (Muñoz-Cobo, 1987; Purroy, 1983). However, the diversity of bird species, especially small insectivorous species, was lower than expected for agricultural areas with small fields in the Mediterranean region (Ceballos & Purroy, 1981; Moral *et al.*, 2002; Marti & Moral 2003).

Study periods

The potato study was conducted between 16 July and 14 August 2002. Conditions in this period are significantly different from those in June, when methamidophos is used on potatoes in Germany. Perhaps most importantly, June is within the peak breeding period for many bird species, and many individuals may have completed breeding by mid-July. Therefore, when assessing this use of methamidophos, most weight should be given to data from earlier in the study, and consideration must be given to how much behaviour might differ in June. For example, more birds may be present during June, and their foraging ranges may be smaller

when they are feeding nestlings: this would increase PT for those birds nesting in or near the field.

The tomato study was conducted earlier, between 18 June and 8 July 2002. Conditions in this study are therefore more relevant to the main period of bird breeding although, as noted above, the crop is less relevant to methamidophos.

Information on the timing of uses of methamidophos other than potatoes in Germany is currently lacking and would be required for a comprehensive assessment.

Adjacent habitats

The notifier selected fields with diverse surrounding habitats, to ensure a high diversity of mammals and birds (Somerville & Walker 1990). While this has advantages, it is also conceivable that the presence of adjacent habitats that are highly attractive relative to the study field might make PT lower than in less diverse landscapes.

Three of the 4 study fields in the potato study had additional fields of potatoes close by. One site in the tomato study had an additional field of tomatoes adjacent to the study field, and 3 of the tomato sites had fields of maize (for which use of methamidophos is supported) adjacent to 3 sides of the study field. These observations emphasise the need for risk assessment to consider the possibility that single individuals could be exposed to multiple treated fields including other supported crops, especially for wide-ranging species such as woodpigeon.

All four fields in the tomato study were close to buildings including farms at 3 sites (2 with loose poultry and one with a pig breeding unit), and housing estates at 2 sites. Human activities associated with the farms and housing are likely to have affected the diversity, abundance, distribution, behaviour and diets of animals in the study, both through providing additional off-field sources of attractive food (there was evidence that some wood mice were taking food from the farm at one site) and through disturbance. This needs to be considered when extrapolating to other areas with less human activity.

Pesticide applications

In the potato study, each study field received one herbicide application prior to the start of observations. Insecticide was applied once to 3 of the potato fields prior to the start of observations; for the other field there was no information. In the tomato study, each study field received 2-3 herbicide applications including some during the observation period. Each tomato field also received 1-2 insecticide applications before the observation period (except that for one field the time of the second application was unknown). Fungicides were applied 5-7 times to the tomato fields and with similar frequency in potatoes. The programs of pesticide applications on the study fields appear broadly consistent with the general growing procedures for the region, based on information from local farmers presented in the notifier's study reports. The timing of herbicide and insecticide applications must be considered when assessing their influence on food availability and PT for particular species of birds and mammals.

Bird censuses

Censuses were conducted on 3 days at each site. In each census, an observer walked around the complete perimeter of the study field and recorded bird numbers and activities in the outer 50-100m of the study field, and also in 50-100m of the immediately adjacent habitat.

The notifier and RMS use the proportions of birds recorded in-crop and off-crop to support their estimates of PT for methamidophos. However, the census data reflect the use of in-crop and off-

crop areas defined by the experimenter, whereas PT should reflect the use by individual animals of different parts of their foraging ranges. In the studies reviewed here, the census area was approximately 50% potatoes and 50% other habitat: this might tend to over-estimate PT (for species with large foraging ranges that typically contain less than 50% potatoes, e.g. woodpigeon) or under-estimate PT (for species with small foraging ranges, so that some individual foraging ranges may contain >50% potatoes, e.g. yellow wagtails in the breeding season).

The census data are also affected by general limitations of studies that use observations of unmarked animals to estimate PT (SANCO, 2002, p. 30). First, it is not possible to determine whether successive observations relate to the same or different individuals, so the distribution of PT between individuals is uncertain. For example, if equal numbers of observations are recorded on and off the field this could mean that all individuals have a PT of 0.5, or that half the individuals have PT=0 and half have PT=1, or an infinite range of other distributions.

Second, if animals are easier to observe in one habitat than the other, the proportions observed in each habitat will be misleading. It is notable that the potato study report states that "in the dense vegetation of potato fields…it was not possible to see if (rabbits) were feeding there". This suggests that visual observations seriously underestimate use of potatoes by most species, except those clearly visible above the crop (i.e. large mammals).

The maps in the potato study report show that the census of the "surrounding" area outside fields 1, 3 and 4 included sections of additional fields of potatoes. Therefore, if the proportions of birds seen in the field and "surroundings" are used to estimate PT, this will lead to under-estimation of the exposure which could occur in the realistic worst case situation where nearby fields are treated with the same pesticide close in time. The same issue affects the tomato study, with the addition that birds recorded in the "surrounding" might have been in maize fields, for which methamidophos is a supported use.

Finally, the number of sites and observation periods is rather small, so there will be substantial sampling uncertainty when extrapolating the results of the census and whole-day observations to other sites and times. This also implies a low chance of observing species that visit fields infrequently, which can nevertheless receive significant exposure in some situations (e.g. flocking or migrating birds).

In summary, the PPR Panel concludes that census data of the type available from these studies are of very limited usefulness for estimating PT. Rather, they provide an approximate indication of the relative intensity of bird use of the areas defined by the experimenter, averaged over an unknown number of individuals. Even this is highly uncertain (e.g. due to limited sample sizes), potentially biased (due to differences in visibility) and may not reflect the relative intensity of feeding in the different areas (as the observations relate to all activities and not just feeding). Therefore, in the PPR's assessment below, the census data are used only qualitatively, together with other information, to inform judgements about relative use of the crop by different species.

Whole day observations of birds

"Whole day" observations were conducted on 2 days at each site, using a modified version of the census methodology. Once per hour during the daylight period, an observer walked around the complete perimeter of the study field and recorded bird numbers and activities in the outer 75m of each potato field, or in the whole of each tomato field.

These observations include only on-field areas and therefore cannot provide a direct measure of PT. They are also subject to the general difficulties affecting visual observations including under-recording, which may be substantial due to the limited visibility in these crops. In

addition, the frequent (almost continuous) presence of experimenters walking around the field perimeter implies that there was frequent disturbance of wildlife present in the field. On the one hand, by causing animals to move this probably increased the visibility of birds and larger mammals (e.g. rabbits, hares). On the other hand, it could also cause animals to leave the field and forage elsewhere, especially those that have large foraging ranges or alternative feeding sites.

Because the observations were made fairly frequently throughout the day, they can provide a qualitative indication of the continuity of bird activity on the field. However, interpretation in terms of PT is very uncertain, because unmarked animals are not individually recognizable. If birds are observed in similar numbers each hour, this may represent the continuous presence of a small number of resident breeding birds, each with PT close (or even equal) to 1. On the other hand, the same data could result from a series of shorter visits by a larger number of different individuals, in which case PT for each individual could be close (but not equal) to zero. General knowledge about the natural history of the species can help to judge which interpretation is more likely, but any such judgement will inevitably be very uncertain. Furthermore, as already mentioned, time spent in the crop may either under- or over-estimate the proportion of diet obtained there. Nevertheless, in the absence of better data (e.g. from marked animals or radio-tracking) the whole-day observations do provide some useful information for a semi-quantitative assessment of PT.

These data can also be used to gain a quantitative impression of average PT for the local population, dividing the average number of birds recorded per observation period by an estimate of the total size of the local population (Fletcher & Greig-Smith, 1988). However, this approach also is uncertain and potentially biased. The average number observed inevitably under-represents the average number present (due to limited visibility). Furthermore, the total size of the local population is unknown and must be estimated from the data. This is inevitably very uncertain, as the true size of the local population could be anywhere between the minimum number observed to be present simultaneously (or less, if some of the birds seen on that occasion are “visitors”) and the maximum observed simultaneously or even more (if PT is low or visibility poor).

In summary, the whole-day observations provide useful information on the continuity of bird presence on the study fields and may help to form judgements about PT, but these are inevitably very uncertain.

Radio-tracking of small mammals

Small mammals were trapped in and around the study fields and tagged with radio transmitters. A total of 13 animals of 3 species were tagged in the potato study and 12 animals of 2 species in the tomato study.

As mentioned earlier, radio-tracking is probably the most useful approach for estimating the proportion of time spent in different habitats. This is because it has the capability to measure directly the proportion of time specific individuals spend in different habitats. However, there are still substantial uncertainties in extrapolating to proportion of diet. The most fundamental is that time spent in crop may under- or over-estimate the proportion of diet obtained in crop. It is possible to obtain better (but still imperfect) estimates, by detecting periods of inactivity (when animals cannot be feeding) and excluding them from the calculation of PT (Crocker *et al.*, 2002), but this was not done in the present studies. Also, only a very small number of individuals per species was radio-tracked, implying substantial sampling uncertainty.

Additional uncertainties were introduced by the specific methodology and reporting of these studies. The reports state that animals were radio-tracked for 24 hours, but do not specify how

these hours were distributed over time (e.g. were they recorded in one session or several and, if the latter, then were they equally distributed over day and night hours?). The reports do not provide sufficient details on where the animals were caught. This information is needed to assess what population the data represent (e.g. primarily an on-field population, or a wider local population), and was provided separately to the PPR Panel by the notifier. When deriving estimates of PT, the time between successive radio-fixes in different habitats was counted entirely as time spent moving between habitats, whereas in fact at least some part of it would be foraging in the crop. This implies that the notifier's estimates of PT are biased towards the low side.

The report of the tomato study used 2 different techniques (minimum convex polygon and kernel) to estimate home ranges and calculate preference indices. The preference indices range between –1 and + 1 and indicate whether the animals used different habitats in proportion to their area within the home range. In principle, evidence of preferences should be helpful, especially when extrapolating to other regions with different habitat composition. However, the preference indices used in this study seem difficult to interpret[43] and less useful for assessing PT than the simple percentage of fixes in the crop.

Information on dietary composition (PD)

The notifier's field studies provide relatively little information relevant to the estimation of PD. The only direct data on dietary composition are stomach contents for 19 small mammals trapped or found in the tomato study in Italy (Table 3): these are discussed in detail in section 3.

Data on the composition and cover of vegetation within the crop were obtained in both the potato and tomato studies, but these indicate what was available to animals rather than what they ate.

Both studies included a small number of incidental observations of birds and mammals collecting or carrying food, but these data are too few to estimate dietary composition with any certainty. In the notifier's study for potatoes in Germany, two instances were recorded of yellow wagtails "bearing caterpillars". In the notifier's study for tomatoes in Italy there was 1 record of a yellow wagtail "flying away with insect", 1 "catching an insect on the ground" and 1 "searching for insects on the ground", plus 5 observations with unspecified food. Of the 8 incidental observations of yellow wagtails feeding in tomatoes, 3 were of birds feeding on the ground. If observations for yellow wagtail are pooled with those for other species (tree sparrow, swallow, stonechat, house sparrow) then there are 18 observations of foraging for insects on the ground (including 10 tree sparrows seen at one time), 1 in the air, and 18 cases where the source of the insect was unknown (e.g. "carrying an insect"). These results show that in these 4 tomato fields at least some insects were taken from the ground, but the sample for yellow wagtails is too small to estimate the proportion of ground feeding with any certainty, the result may be biased if birds feeding on the plants are less visible than those in between the rows, and there would be further uncertainty in extrapolating this to those crops supported for methamidophos.

[43] For example: of 2 wood mice which had 100% of their radio-fixes inside the tomato fields, one had a preference index of –0.6 by the polygon method and +0.9 by the kernel method; while the other had indices of zero by both methods.

Table 3. Identity numbers and stomach contents of 17 wood mice caught by snap-trapping in the notifier's field study in tomatoes. Stomach contents were classified but not quantified.

Individuals with only type of material identified	Description of contents
22-0307-03	Insects
32-2606-01	Animal remains, maybe slugs
23-0307-02	Earthworm
33-2606-03	Earthworms (30-40 vol%)
22-3006-03	Plants, maybe berries
23-3006-04	Green parts of plants
22-0107-02	Seeds or corn
22-0307-01	Seeds or corn
22-3006-02	Seeds or corn, starch
21-0207-01	Seeds or corn, starch
23-0107-03	Starch (probably from corn)
22-3006-01	Starch (probably from corn)
Individuals with >1 type of material identified	
33-2606-02	Animal remains, earthworm and maybe insect larvae
23-2806-01	Insects, seeds or corn, starch
22-0107-05	Berries, a little bird feather
21-0107-01	Seeds or corn, starch, green parts of plants
22-0107-04	Starch, fruits

The tomato study included estimates of the range and speed of movement of radio-tracked small mammals within the field. The average speed of movement of radio-tracked mice was 81 m/h inside potato fields (n=4, but 51 m/h for the 3 individuals which spent significant time in the crop) and 30 m/h inside tomato fields (n=8). The notifier comments that these speeds suggest that wood mice were foraging for foods that were "rare" (thinly distributed) rather than concentrated in patches.

APPENDIX 2 - DETAILED EVALUATION OF STUDIES RELEVANT TO ASSESSING AVOIDANCE

One-day feeding study with bobwhite quail (Barfknecht, 2001)

Bobwhite quail aged approximately one year were housed singly indoors (18-20°C, 8h/d light period) with *ad libitum* standard quail diet for 8 days, then offered for one test day the same diet treated with technical methamidophos at measured concentrations of 9, 31, 98, 316 and 846 mg a.s./kg diet (10 birds per concentration plus 10 with untreated diet), then returned to untreated diet for 7 days. Birds were observed for signs of intoxication continually on the test day and once daily thereafter. Food consumption was measured daily, body weight at the beginning and end of the test day and at the end of the study.

Details of the experimental design can greatly influence the outcome of feeding studies and need to be reported clearly so that they can be taken into account. For example, in this study:

- The precise nature of the food container is unclear (it was described as a "feeder" and "feeding box". Depending on the design of this container, vapour concentrations above it

may have been greater than would be expected in the field and might cause an exaggerated avoidance response (Fryday *et al*., 1998).
- Birds were observed "continually" on the test day but it is not stated whether precautions were taken to avoid disturbance (e.g. concealment of the observer). Continuous presence of an observer might cause fragmentation of feeding into many short bouts, and increase the chance of avoidance responses developing before a lethal dose is ingested.
- The study report states that the test diet was stored frozen and "thawed immediately before exposure" but gives no further details. If the food was significantly below ambient temperature at the time of presentation, this could have affected the initial rate of consumption.

The results of this study showed strong avoidance (AV, consumption as a proportion of consumption in the control group) starting between 9 and 31 mg a.s./kg diet (Figure 6). The notifier and RMS used these results to fit a regression relationship between the concentration of methamidophos in food and AV (curved solid line in Figure 6, equation in legend). The notifier and RMS used this relationship to estimate AV in their risk assessments for yellow wagtail and wood pigeon, adjusted to the concentrations estimated for the field.

The PPR Panel has used the same results to plot the average ingested dose (consumption x concentration / body weight) for each concentration (Figure 7; the notifier and RMS also show a graph similar to this). The graph also shows for comparison the dose expected if there were no avoidance (control group consumption x concentration), the LD50 reported from a separate study with this species (10.54 mg a.s./kg body weight[44], Nelson 1979a), and the numbers of birds showing sublethal and lethal effects. The effects seen in this study were diarrhoea at all doses starting from 31 mg a.s./kg, and apathy, discoordinated movements and reduced vigilance at 316 and 846 mg a.s./kg.

Figure 7 allows various insights into the possible mechanisms underlying the results. It shows that, at higher concentrations, the degree of avoidance increases such that the ingested dose remains roughly constant and well below the LD50. This pattern has also been reported for some other anticholinesterase compounds (e.g. Bennett, 1989). It suggests that, under the conditions in this study, the avoidance response of bobwhite quail enables them to control their exposure to methamidophos. The fact that the maximum dose consumed by the birds in this study was so far below the LD50 suggests that (a) the dose threshold for sublethal effects (and avoidance) was well below the lethal dose (as was also seen in the LD50 study with this species), and (b) the birds were unable to metabolise methamidophos rapidly – otherwise the dose ingested over a day could rise above acute (gavage) LD50 without causing mortality (as occurred in the study with mice, see later).

During the first three days after the test day, food consumption was very similar in all groups including the control animals. This suggests that the birds rapidly resumed normal feeding when presented with clean food, although a precise time cannot be given because consumption was only measured for the 3 days combined.

[44] Geometric mean of LD50s for males (10.1) and females (11.0), as used by notifier and RMS. Note that the purity of the technical active substance in this test was 75% but no correction is made for this, because it appears that the technical active substance used in the formulation has similar purity (73%, DAR Vol 1, section 1.3.5).

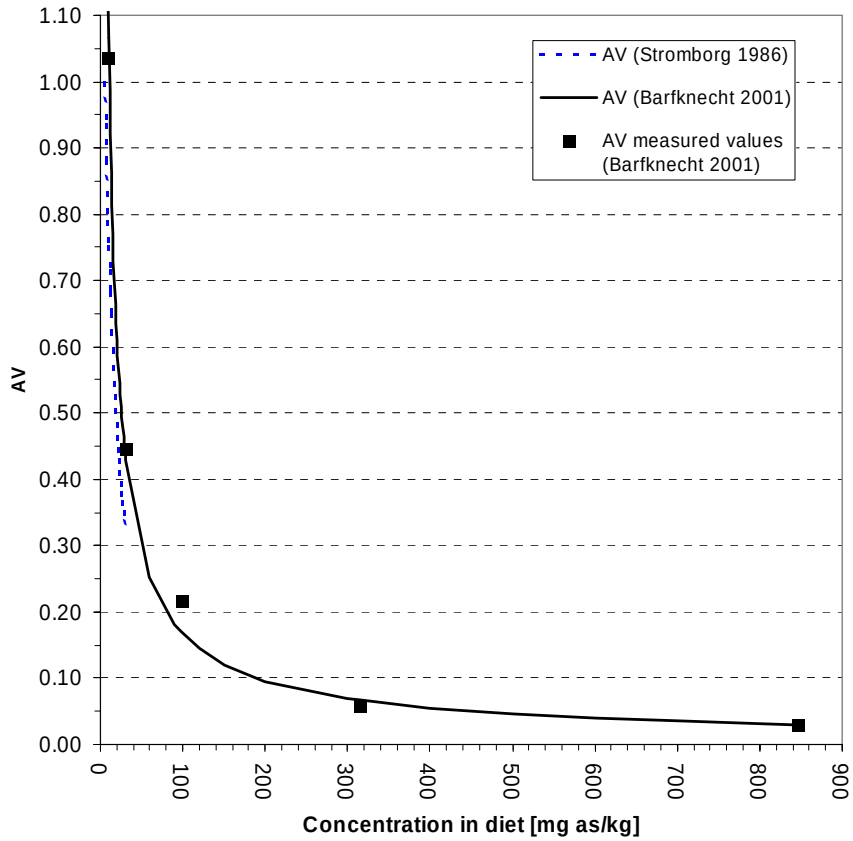

Figure 6. Relationship between concentration of methamidophos in the diet and food avoidance (AV) in 2 studies with bobwhite quail (Barfknecht 2001 and Stromborg 1986). The regression equation for the solid line is AV=6.8 x Concentration$^{-0.805}$ and fits the data closely (R^2 = 0.9893).

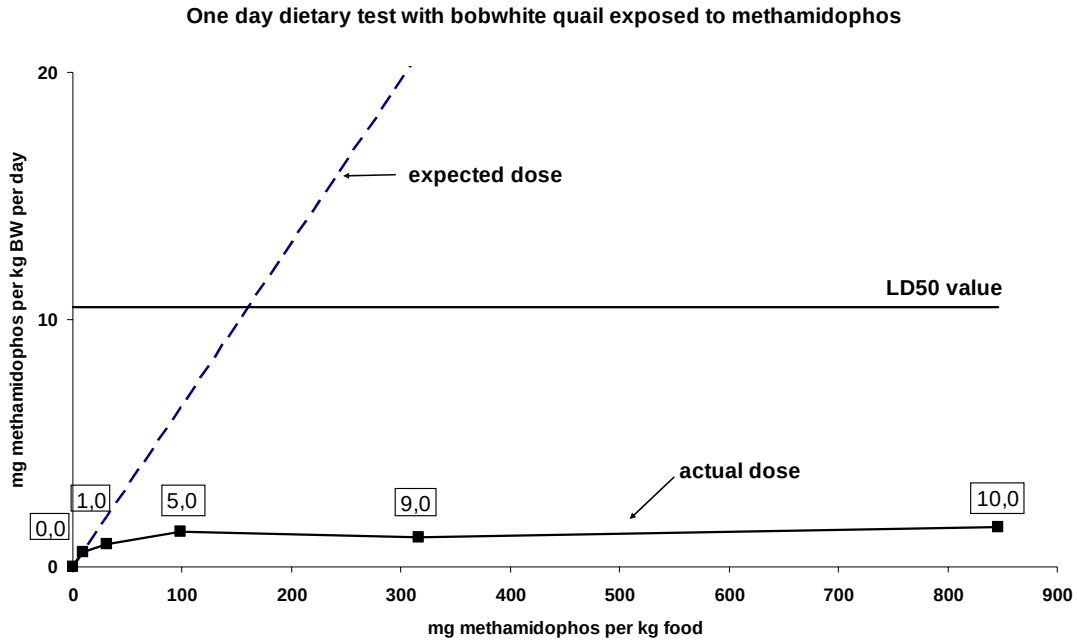

Figure 7. Relationship between measured concentrations of methamidophos in the diet and the dose ingested in a 1 day feeding study with 1 year old bobwhite quail (Barfknecht, 2001). The diagonal line shows the dose expected if there were no avoidance. The horizontal line shows the acute gavage LD50 reported from another study with the same species. The numbers in boxes represent the number of birds showing sublethal and lethal effects at each concentration (e.g. [5,0] signifies 5 birds with sublethal effects and 0 mortalities).

Modified avian reproduction study (Stromborg, 1986)

In a modified avian reproduction study, pairs of first year breeding bobwhite quail were housed indoors (15h/d light period) and offered) for 15 test days standard game bird diet treated with constant or variable concentrations of methamidophos (purity not stated). A third set of birds ("pair-fed") were given untreated food but the amounts provided were set equal to those consumed by the birds on the constant concentrations. There were 5 levels of constant concentrations at 5, 7.8, 12.3, 19.2 and 30 mg/kg diet (5 pairs per level). Two of the 10 birds at the highest constant concentration died between days 11-15, and also one of the 10 birds in the corresponding "pair-fed" group: the author concluded that starvation probably accounted for these deaths.

The notifier and RMS fitted a regression relationship between avoidance and concentration for the constant concentration groups in this study (Figure 6). This is closely similar to that obtained in the 1-day study of Barfknecht (2001).

Five-day LC50 study with bobwhite quail (Wildlife International Ltd, 1979)

In a typical avian dietary LC50 study, bobwhite quail aged 14 days were housed indoors (14h/d light period) and offered for 5 test days standard game bird starter diet treated with technical methamidophos (purity 74%) at nominal concentrations of 5.62, 10, 17.8, 31.6 and 56.2 mg a.s./kg diet (10 birds per concentration, plus 5 pens of 10 birds with untreated diet), then returned to untreated diet for 3 days. Feeder design was not reported. Birds were observed for signs of intoxication once daily. Food consumption for the whole 5 day test period was measured by pen, body weight at the beginning and end of the study. Consumption was not reported for the post-test period, so it is not possible to estimate how rapidly the survivors resumed normal feeding.

Results from this study are summarised in Figure 8. Substantial avoidance started at similar concentrations to the one day study with year-old bobwhites (about 30 mg a.s./kg, Figures 6 and 7). The ingested dose reaches a plateau close to the LD50, much higher than in Figure 7. Factors that could contribute to this include: the LD50 may differ for younger birds; the threshold for sublethal effects (and avoidance) may be closer to the LD50 for younger birds; and increasing hunger over the longer exposure period (5d vs. 1d). As birds on the highest treatment were receiving approximately one lethal dose per day, this and their reduced food consumption may both have contributed to the mortalities, which started on the third test day and continued through to day 8. Starvation may also have contributed to the 2 mortalities on the second-highest treatment, which both occurred in the post-test period, because consumption was measured for the group as a whole and may have been much lower for some individuals. Sublethal effects at the two highest concentrations included lethargy, loss of coordination and lower limb weakness. Surviving birds were asymptomatic by day 8.

Hill & Camardese (1986) summarise a 5 day dietary LC50 study for methamidophos with another species of quail, *Coturnix coturnix japonica*. This also shows substantial avoidance at concentrations above the LC50, with mortalities starting at day 3.

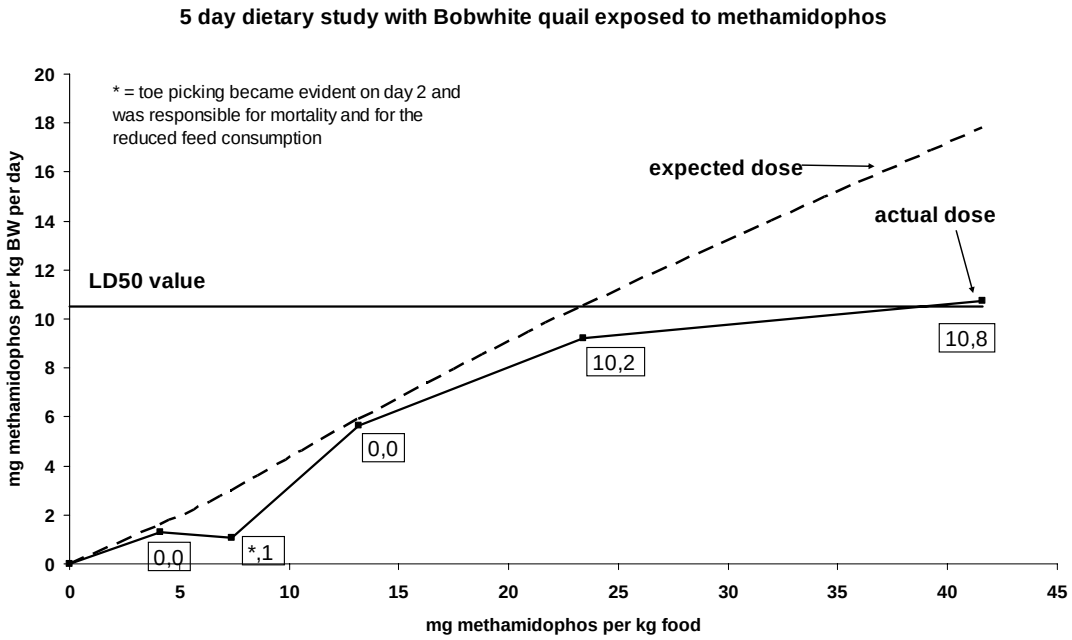

Figure 8. Relationship between concentration of methamidophos in the diet (corrected for purity of 74%) and the average dose ingested in a 5 day LC50 study with 14 day old bobwhite quail (Wildlife International Ltd, 1979). See Figure 7 for explanation. The expected dose line reaches the LD50 at a lower concentration in this study, due to the higher ratio of food intake to body weight in 14 d old birds.

Five-day LC50 study with mallard duck (Nelson, 1979b)

In a typical avian dietary LC50 study, mallard ducks aged 10 days were housed indoors (24h/d light period) and offered for 5 test days standard game bird starter diet treated with technical methamidophos (purity 75%) at nominal concentrations of 380, 531, 744, 1041, 2040, 2857 and 4000 mg a.s./kg diet (10 birds per concentration, plus 5 pens of 10 birds with untreated diet), then returned to untreated diet for 3 days. Feeder design was not reported. Birds were observed for signs of intoxication once daily. Food consumption was measured daily by pen, body weight at the beginning and end of the study.

Results from this study are summarised in Figure 9. Because consumption was measured daily, the doses ingested on test days 1-5 can be plotted separately. There was substantial avoidance at all tested concentrations and, on the higher treatments, the degree of avoidance increased from day 1 to day 5. Mortalities at the two lowest concentrations occurred on days 5-6: given the strong avoidance these may be due primarily to starvation. Mortalities at the higher doses presumably result from toxicity, as they occurred in the first 2 days and the average dose of these groups was close to or above the LD50 on day 1. On the 2 highest treatments mortalities occurred on the first day, and it appears the concentration was so high that birds consumed an acute lethal dose before the avoidance response set in. Ataxia occurred in all treatment groups but survivors were asymptomatic by the 4th test day, despite their continuing exposure.

Food consumption rose sharply to a similar level for all treated groups (average 58.5 – 69 g/bird) on the first day of the post-exposure period. Although lower than the controls (90 g/bird) this reflects the lower body weight of the treated birds at this time (average 110 – 126 g compared to 350 g for controls). These results suggest that the birds resumed normal feeding rapidly (within at most a few hours) when presented with clean food.

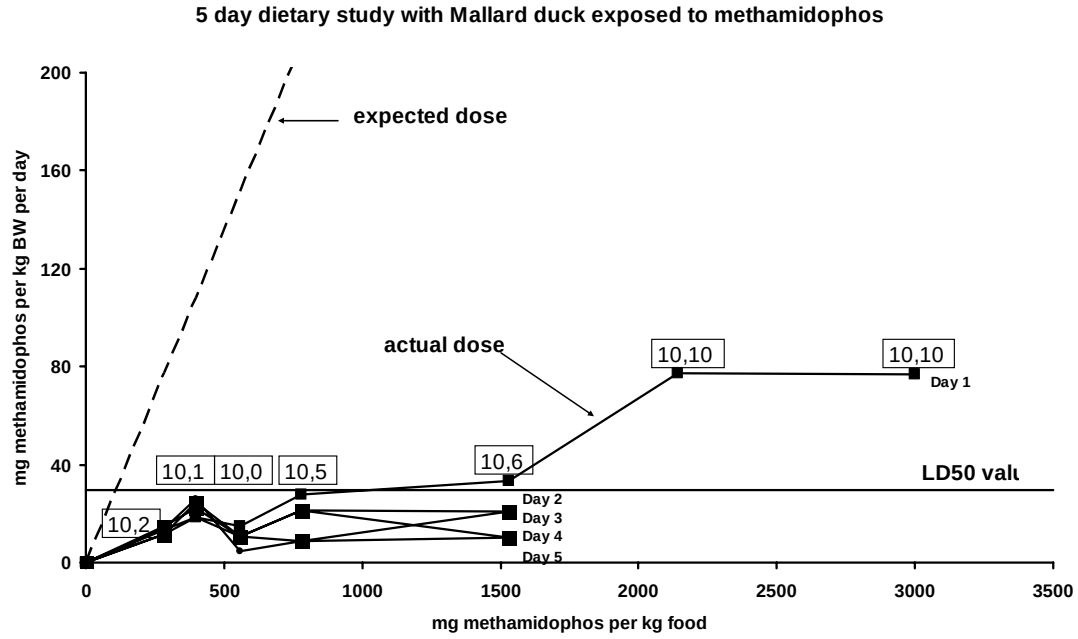

Figure 9. Relationship between concentration of methamidophos in the diet (corrected for purity of 74%) and the average dose ingested in a 5 day LC50 study with 10 day old mallard ducks (Nelson, 1979b). See Figure 7 for explanation. The LD50 in this graph is for mallard duck (29.5 mg/kg BW), from Pesticide Manual, 11th edition, (ed. C. Tomlin).

Acute LD50 study with bobwhite quail (Nelson, 1979a)

In a typical acute LD50 study, bobwhite quail aged 22 weeks were dosed orally at 2.2, 4.7, 10.1, 21.8 or 47.1 mg methamidophos (75% purity)/kg body weight (10 males and 10 females at each dose). The LD50 was reported as 10.1 mg/kg for males and 11.0 mg/kg for females (not corrected for purity). The interesting aspect with respect to avoidance is that sublethal effects (lethargy) and reduced feed consumption (average 14% of control for females and 21% for males) were observed on day of treatment in the 2.2 mg/kg treatment groups, suggesting that, for this species under these conditions, avoidance responses occur at doses well below the LD50. These treatment groups were asymptomatic "within day 2" (where day 0 = day of

dosing) and their food consumption had increased to 69-81% of control. Higher treatment groups resumed normal feeding more gradually: the 4.7 mg a.s./kg group first exceeded 50% of control consumption on day 3 whereas the 10.1 mg a.s./kg group did so on day 5.

One-day feeding test with mice (Brendler-Schwaab, 2001)

CD-1 mice aged 9 weeks were housed singly indoors (22°C, 12h/d light period) and acclimatized to the test room for at least 5 days with untreated meal diet, then offered for one test day the same diet treated with technical methamidophos at nominal concentrations of 0, 50, 158, 500, 1580 and 5000 mg a.s./kg diet (5 mice per concentration, measured concentrations were 82-102% of nominal), then returned to untreated diet for 13 days. Animals were observed for signs of intoxication once daily. Food consumption and body weight were measured for the test day (day 1), and also on days –1, 6 and 13.

The results of this study showed strong avoidance (AV, consumption as a proportion of consumption in the control group) starting between 50 and 158 mg a.s./kg diet (Figure 10). The notifier and RMS used these results to fit a regression relationship between the concentration of methamidophos in food and AV (curved solid line and equation in Figure 6). The notifier and RMS used this relationship to estimate AV in their risk assessments for wood mouse, adjusted to the concentrations estimated for the field.

The PPR Panel used the same results to plot the average ingested dose for each concentration (Figure 11). The graph also shows the dose expected if there were no avoidance, the highest and lowest LD50s reported from separate studies with mice, and the numbers of mice showing sublethal and lethal effects. At 158 mg a.s./kg, 2 mice showed apathy and 1 tremors, on day 1 only. At 500 mg a.s./kg a variety of effects were seen including tremors, apathy, laboured breathing, staggering gait and decreased reactivity, lasting 1-4 days, and 1 mortality.

Unlike the results for quail (Figure 7) the ingested dose for mice rises above the acute oral LD50, suggesting that mice can metabolise methamidophos more rapidly than quail and therefore tolerate an increased dose over a 1d period. The dose threshold for avoidance seems to be around half the LD50, rather higher than in quail (Figure 7).

During the first six days after the test day, there was no statistically significant difference between food consumption of treated and control groups although there was a non-significant trend for reduced consumption in the higher treatment groups. It cannot be determined how rapidly the survivors resumed normal feeding when presented with clean food, because consumption was only measured for the 6 days combined.

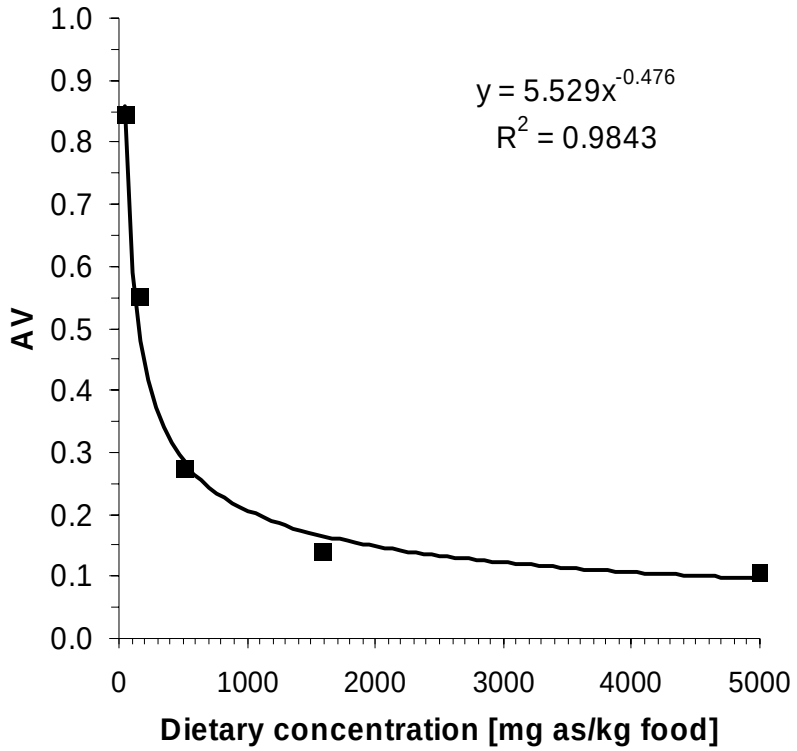

Figure 10. Correlation between avoidance factor (AV) and dietary concentrations of methamidophos in a one day feeding study with mice (Brendler-Schwaab, 2001).

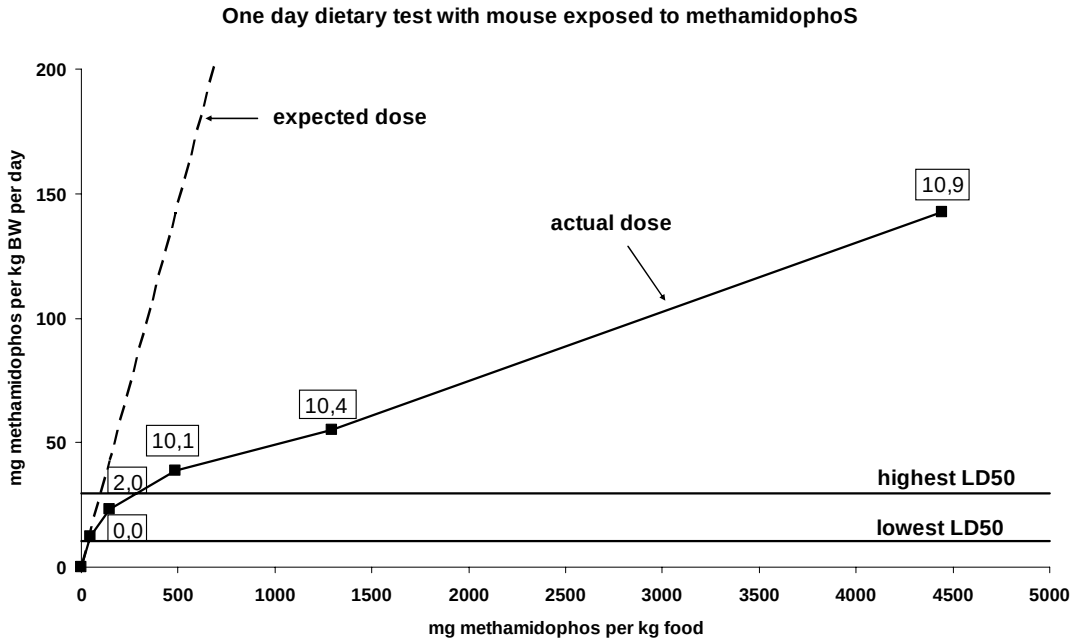

Figure 11. Relationship between measured concentrations of methamidophos in the diet and the dose ingested in a 1 day feeding study with 9 day old mice (Brendler-Schwaab, 2001). See Figure 7 legend and text for explanation. LD50s for mouse 10.5 – 29.6 mg/kg BW, from: http://ecb.jrc.it/classlab/4300a43_IT_metamidophos.doc

EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate D - Food Safety: Production and distribution chain
Unit D.3 - Chemicals, contaminants and pesticides

Review report for the active substance **methamidophos**

Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 3 March 2006
in view of the inclusion of methamidophos in Annex I of Directive 91/414/EEC

1. Procedure followed for the re-evaluation process

This review report has been established as a result of the re-evaluation of methamidophos, made in the context of the work programme for review of existing active substances provided for in Article 8(2) of Directive 91/414/EEC concerning the placing of plant protection products on the market, with a view to the possible inclusion of this substance in Annex I to the Directive.

Commission Regulation (EEC) No 3600/92([1]) laying down the detailed rules for the implementation of the first stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC, as last amended by Regulation (EC) No 2266/2000([2]), has laid down the detailed rules on the procedure according to which the re-evaluation has to be carried out. Methamidophos is one of the 90 existing active substances covered by this Regulation.

In accordance with the provisions of Article 4 of Regulation (EEC) No 3600/92, United Phosphorus Ltd on 26 July 1993, K & N Efthymiadis SA on 19 July 1993, Marubeni UK PLC on 23 July 1993, Bayer AG on 21 July 1993, Tomen France SA on 22 July 1993, Iberotam on 26 July 1993, Industrias Quím´cas del Vallés on 28 July 1993, Pilar Ibérica SL on 23 July 1993, Helm AG on 23 July 1993 and B.V. Luxan on 21 July 1993 notified to the Commission of their wish to secure the inclusion of the active substance methamidophos in Annex I to the Directive.

In accordance with the provisions of Article 5 of Regulation (EEC) No 3600/92, the Commission, by its Regulation (EEC) No 933/94([3]), as last amended by Regulation (EC) No 2230/95([4]), designated Italy as rapporteur Member State to carry out the assessment of methamidophos on the basis of the dossiers submitted by the notifiers. In the same Regulation, the Commission specified furthermore the deadline for the notifiers with regard to the submission to the rapporteur Member States of the dossiers required under Article 6(2) of

[1] OJ No L 366, 15.12.1992, p.10.

[2] OJ No L 259, 13.10.2000, p.27.

[3] OJ No L 107, 28.04.1994, p.8.

[4] OJ No L 225, 22.09.1995, p.1.

Regulation (EEC) No 3600/92, as well as for other parties with regard to further technical and scientific information; for methamidophos this deadline was 31 October 1995.

Only Bayer/Tomen submitted in time a dossier to the rapporteur Member State which did not contain substantial data gaps, taking into account the supported uses. Therefore Bayer/Tomen was considered to be the main data submitter.

In accordance with the provisions of Article 7(1) of Regulation (EEC) No 3600/92, Italy submitted on 23 August 2000 to the Commission the report of its examination, hereafter referred to as the draft assessment report, including, as required, a recommendation concerning the possible inclusion of methamidophos in Annex I to the Directive. Moreover, in accordance with the same provisions, the Commission and the Member States received also the summary dossier on methamidophos from Bayer/Tomen, on 27 November 2000.

In accordance with the provisions of Article 7(3) of Regulation (EEC) No 3600/92, the Commission forwarded for consultation the draft assessment report to all the Member States on 19 September 2000 as well as to Bayer/Tomen being the main data submitter, on 19 January 2001.

The Commission organised an intensive consultation of technical experts from a certain number of Member States, to review the draft assessment report and the comments received thereon (peer review), in particular on each of the following disciplines:

- identity and physical /chemical properties ;
- fate and behaviour in the environment ;
- ecotoxicology ;
- mammalian toxicology ;
- residues and analytical methods ;
- regulatory questions.

The meetings for this consultation were organised on behalf of the Commission by the Biologische Bundesanstalt für Land und Forstwirtschaft (BBA) in Braunschweig, Germany, from March to September 2001.

The meetings for this consultation were also organised on behalf of the Commission by the Pesticide Safety Directorate (PSD) in York, United Kingdom, from February to September 2003.

The report of the peer review (i.e. full report) was circulated, for further consultation, to Member States and the main data submitter on 16 November 2001 for comments and further clarification.

In accordance with the provisions of Article 6(4) of Directive 91/414/EEC concerning consultation in the light of a possible unfavourable decision for the active substance the Commission organised a tripartite meeting with the main data submitter and the rapporteur Member State for this active substance on 20 February 2004.

In accordance with the provisions of Article 7(3) of Regulation (EEC) No 3600/92, the dossier, the draft assessment report, the peer review report (i.e. full report) and the comments and clarifications on the remaining issues, received after the peer review were referred to the **Standing Committee on the Food Chain and Animal Health**, and specialised working groups

of this Committee, for final examination, with participation of experts from all Member States. This final examination took place from November 2003 to July 2005.

These documents were also submitted to EFSA's Scientific Panel on Plant Health, Plant Protection Products and their Residues for separate consultations. The reports of this Panel were formally adopted on 14 September and 14 December 2004 (Questions FSA-Q-2004-60 and Q-2004-59)[5]

The present review report was finalised in the meeting of the **Standing Committee** on 3 March 2006. It contains the conclusions of the final examination; given the importance of the draft assessment report, the peer review report (i.e. full report) and the comments and clarifications submitted after the peer review as basic information for the final examination process, these documents are considered respectively as background documents A, B and C to this review report and are part of it.

2. Purposes of this review report

This review report, including the background documents and appendices thereto, has been developed and finalised in support of the Directive **2006/131/EC**[6] concerning the inclusion of methamidophos in Annex I to Directive 91/414/EEC, and to assist the Member States in decisions on individual plant protection products containing methamidophos they have to take in accordance with the provisions of that Directive, and in particular the provisions of article 4(1) and the uniform principles laid down in Annex VI.

This review report provides also for the evaluation required under Section A.2.(b) of the above mentioned uniform principles, as well as under several specific sections of part B of these principles. In these sections it is provided that Member States, in evaluating applications and granting authorisations, shall take into account the information concerning the active substance in Annex II of the directive, submitted for the purpose of inclusion of the active substance in Annex I, as well as the result of the evaluation of those data.

In accordance with the provisions of Article 7(6) of Regulation (EEC) No 3600/92, Member States will keep available or make available this review report for consultation by any interested parties or will make it available to them on their specific request. Moreover the Commission will send a copy of this review report (not including the background documents) to all operators having notified for this active substance under Article 4(1) of this Regulation.

The information in this review report is, at least partly, based on information which is confidential and/or protected under the provisions of Directive 91/414/EEC. It is therefore recommended that this review report would not be accepted to support any registration outside the context of Directive 91/414/EEC, e.g. in third countries, for which the applicant has not demonstrated to have regulatory access to the information on which this review report is based.

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[5] Opinions of the Scientific Panel on Plant Health, Plant Protection Products and their Residues on requests from the Commission related to the evaluation of methamidophos in toxicology and ecotoxicology in the context of Council Directive 91/414/EEC (*The EFSA Journal* (2004), 95, 1-15 adopted on 14 September 2004 and Journal (2004) 144, 1-50 adopted on 14 December 2004).

[6] OJ No L 349, 12.12.2006, p.17.

3. Overall conclusion in the context of Directive 91/414/EEC

The overall conclusion from the evaluation is that it may be expected that plant protection products containing methamidophos will fulfil the safety requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC. This conclusion is however subject to compliance with the particular requirements in sections 4, 5, 6 and 7 of this report, as well as to the implementation of the provisions of Article 4(1) and the uniform principles laid down in Annex VI of Directive 91/414/EEC, for each methamidophos containing plant protection product for which Member States will grant or review the authorisation.

Furthermore, these conclusions were reached within the framework of the uses which were proposed and supported by the main data submitter and mentioned in the list of uses supported by available data (attached as Appendix IV to this Review Report).

Extension of the use pattern beyond those described above will require an evaluation at Member State level in order to establish whether the proposed extensions of use can satisfy the requirements of Article 4(1) and of the uniform principles laid down in Annex VI of Directive 91/414/EEC.

With particular regard to residues, the review has established that the residues arising from the proposed uses, consequent on application consistent with good plant protection practice, have no harmful effects on human or animal health. The Theoretical Maximum Daily Intake (TMDI; excluding water) for a 60 kg adult is 17 % of the Acceptable Daily Intake (ADI), based on the FAO/WHO European Diet (WHO 1998). The National Estimated Short Term Intake (NESTI) for a 14.5 kg toddler ranges from 10 to 70 % of the Acute Reference Dose (ARfD), based on the UK diet (PSD, 1999). Additional intake from water and products of animal origin are not expected to give rise to intake problems.

The review has identified acceptable exposure scenarios for operators, workers and bystanders, which require however to be confirmed for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles.

The review has also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC, provided that certain conditions are taken into account as detailed in section 6 of this report.

4. Identity and Physical/chemical properties

The main identity and the physical/chemical properties of methamidophos are given in Appendix I.

The active substance shall comply with the FAO specification and there seem not to be reasons for deviating from that specification; the FAO specification is given in Appendix I of this report.

The review has established that for the active substance notified by the main data submitter Bayer/Tomen, none of the manufacturing impurities considered are, on the basis of information currently available, of toxicological or environmental concern.

In accordance with the provisions of Article 13(5) of Directive 91/414/EE, and considering point 5.2 of the guidance document on equivalence of technical materials (SANCO/10597/2003 – rev. 7), the substance notified by the other data submitter (Sinon EU Corporation, to whom K & N Efthymiadis SA transferred its business for methamidophos on 17 October 1997), on the basis of the information currently available, deviates significantly from the impurity profiles of Bayer/Tomen, in the meaning of Article 13(2) of the Directive. However, the substance submitted by Sinon EU Corporation shall comply with the FAO specification.

5. Endpoints and related information

In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 4(1) of Directive 91/414/EEC and the uniform principles laid down in Annex VI of that Directive, the most important endpoints were identified during the re-evaluation process. These endpoints are listed in Appendix II.

6. Particular conditions to be taken into account on short term basis by Member States in relation to the granting of authorisations of plant protection products containing methamidophos

On the basis of the proposed and supported uses (as listed in Appendix IV), the following particular issues have been identified as requiring particular and short term attention from all Member States, in the framework of any authorisations to be granted, varied or withdrawn, as appropriate:

- Only uses as insecticide on potato may be authorised.

  The following conditions of use must be respected:

- At rates not exceeding 0,5kg active substance per hectare per application.
- Maximum 3 applications per season.

  The following uses must not be authorised:

- Air application;
- Knapsack and all hand-held aapplications, neither by amateur nor by professional users;
- Home gardening.

Member States shall ensure that all appropriate risk mitigation measures are applied and must pay particular attention to the protection of:

– birds and mammals. Conditions of authorisation shall include risk mitigation measures, such as a judicious timing of the application and the selection of those formulations which, as a result of their physical presentation or the presence of agents that ensure an adequate avoidance, minimise the exposure of the concerned species;

– aquatic organisms and non target arthropods and an appropriate distance must be kept between treated areas and surface water bodies as well as margins of the crop. This distance may depend on the application or not of drift reducing techniques;

– operators, who must wear suitable protective clothing during mixing-loading and gloves, coveralls, rubber boots and face protection or safety glasses during application and cleaning of equipment. The above measures must be applied, unless the exposure to the substance is adequately precluded by the design and construction of the equipment itself or by the mounting of specific protective components on such equipment.

7. List of studies to be generated

Member States shall request the submission of further studies to confirm the risk assessment for birds and mammals. They shall ensure that the notifiers at whose request methamidophos has been included in Annex I of Council Directive 91/414/EEC provide such studies to the Commission within 1 year from the entry into force of the Directive of inclusion.

Member States must ensure that the authorisation holders report at the latest on 31 December of each year on incidences of operator health problems, require sales data and a survey of use patterns so that a realistic picture of the use conditions and the possible toxicological impact of methamidophos can be obtained.

8. Information on studies with claimed data protection

For information of any interested parties, Appendix III gives information about the studies for which the main data submitter has claimed data protection and which during the re-evaluation process were considered as essential with a view to annex I inclusion. This information is only given to facilitate the operation of the provisions of Article 13 of Directive 91/414/EEC in the Member States. It is based on the best information available to the Commission services at the time this review report was prepared; but it does not prejudice any rights or obligations of Member States or operators with regard to its uses in the implementation of the provisions of Article 13 of the Directive 91/414/EEC neither does it commit the Commission.

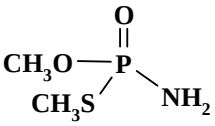
9. Updating of this review report

The technical information in this report may require to be updated from time to time in order to take account of technical and scientific developments as well as of the results of the examination of any information referred to the Commission in the framework of Articles 7, 10 or 11 of Directive 91/414/EEC. Such adaptations will be examined and finalised in the **Standing Committee on the Food Chain and Animal Health**, in connection with any amendment of the inclusion conditions for methamidophos in Annex I of the Directive.

APPENDIX I

Identity, physical and chemical properties

METHAMIDOPHOS

Common name (ISO)	Methamidophos
Chemical name (IUPAC)	O,S-dimethyl phosphoramidothioate
Chemical name (CA)	O,S-dimethyl phosphoramidothioate
CIPAC No	355
CAS No	10265-92-6
EEC No	015-095-00-4 (233-606-0)
FAO SPECIFICATION	FAO Specification AGP:CP/320 (1995). The methamidophos content shall be declared (not less than 680 g/kg) and, when determined, the content obtained shall not differ from that declared by more than ± 25 g/kg.
Minimum purity	730 g/kg min. ECCO 109 did not considered necessary to change the FAO specification as the toxicological studies cover all impurities.
Molecular formula	$C_2H_8NO_2PS$
Molecular mass	141.1
Structural formula	

Melting point	Test material: batch-no.: 920914ELB01 (purity 99.5%) Results: 45 °C.
Boiling point	Not measurable, decomposition above 160°C
Appearance	Pure active ingredient: crystals Active substance as manufactured: liquid or crystal slurry.
Relative density	Test material: batch-no.: 920914ELB01 (purity 99.5%) Results: 1.27 g/cm^3 at 20 °C Results: Tamaron SL 200 Blue D_4^{20}=1.170.
Vapour pressure	Test material: batch-no.: 870716ELB05 (purity 99.5%) Results: 2.3 x 10^{-5} h Pa at 20°C.
Henry's law constant	(a) H < 1.6 x 10^{-6} Pa x m^3 x mol^{-1} (b) Not available
Solubility in water	Test material: batch-no.: APF09028750 (purity 99.5%) Results: > 200 g/l at 20 °C.
Solubility in organic solvents	Test material: batch-no.: KRJ031180 (purity 99.5%) not on active substance as manufactured. Results: n-Hexane < 1 g/l at 20 °C Toluene 2 - 5 g/l at 20 °C Dichloromethane > 200 g/l at 20 °C 2 - Propanol > 200 g/l at 20 °C Acetone > 200 g/l at 20 °C Dimethylformamide > 200 g/l at 20 °C
Partition co-efficient (log P_{ow})	Test material: batch-no.: APF21088500 (purity 99.7%) Results: logP_{ow} = -0.80 at 20 °C

Hydrolytic stability (DT_{50})	Test material: batch-no.: KRJ230184 (purity 99.3%) Results: Half-life of methamidophos in aqueous buffer at 22°C (extrapolated) pH 4: 660 d pH 7: 5 d pH 9: 3 d Test material: [S-methyl-14C]-methamidophos (radiochemical purity: >98%; specific activity: 25.7 mCi/mmol) Results: Half-life of methamidophos in aqueous buffer at 25°C (extrapolated) pH 5: 309 d pH 7: 27 d pH 9: 3 d Hydrolysis products; methyldisulfanylmethane, thiophosphoric acid, O,S-dimethyl ester, thiophosphoramidic acid, S-methyl ester.
Dissociation constant	Methamidophos has neither basic nor acidic properties in water. Thus it is not possible to determine a pK value
Quantum yield of direct photo-transformation in water at λ >290 nm	Test material: batch-no.: 900208ELB01 (purity 99.0%) Results: The UV absorption data showed that methamidophos in aqueous solution does not absorb any light at wavelengths above about 250 nm. The determination of the quantum yield in order to estimate the environmental half-life makes no sense in this case, because no contribution of the direct photodegradation to the overall elimination of methamidophos in the environment is expected.
Flammability	Test material: Active substance as manufactured - (batch no.: 278567036/1, purity 75.4 %) Results: Tamaron TA is not highly flammable in the sense of EU Guideline A.10. Test material: Active substance as manufactured - (batch no.: 278567036/1, purity 75.4 %) Results: Ignition point: 320 °C.
Explosive properties	Test material: Active substance as manufactured - (batch no.: 278567036/1, purity 75.4 %) Results: Tamaron TA is not explosive in the sense of EU Guideline A.14.
UV/VIS absorption (max.)	max 217.4 nm
Photostability in water (DT_{50})	Test material: [S-methyl-14C]-methamidophos (radiochemical purity: >98%; specific activity: 25.7 mCi/mmol) Results: Photodecomposition was first-order and yielded half-life values of 37 days in continuous simulated sunlight

	and 90 days under natural sunlight (Kansas USA, latitude 38°49', longitude 94°40', 320 m above sea level). The differences between the two systems were therefore largely attributable to the period of irradiation (24-hour vs. 12-hour days). In both systems, the primary photolysis products were desmethyl methamidophos and deamidated methamidophos. An additional unknown photolysis product was observed in both systems, but did not exceed 2% of the applied radioactivity.

APPENDIX II

END POINTS AND RELATED INFORMATION

METHAMIDOPHOS

1 Toxicology and metabolism

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	Methamidophos is rapidly absorbed.
Distribution:	Widely distributed.
Potential for accumulation:	None.
Rate and extent of excretion:	50-60%, based on urinary excretion within 24 hours; at day 28 after intragastric administration 80-90% of methamidophos is excreted mainly via urine (60-70%) and via faeces.
Toxicologically significant compounds:	Parent compound.
Metabolism in animals:	Methamidophos is metabolised to several compounds: desamino-methamidophos, monomethyl phosphate, methylphosphoramidate, S-methylphosphoramidothioate and phosphoric acid.

Acute toxicity

Rat LD_{50} oral:	Males: 11.8 mg/kg bw; Females: 10.5 mg/kg bw
Rat LD_{50} dermal:	50 mg/kg bw
Rat LC_{50} inhalation:	Males: 63.2 mg/m^3; Females: 76.5 mg/m^3
Skin irritation:	Slightly irritant (rabbit)
Eye irritation:	Slightly irritant
Skin sensitization (test method used and result):	Not sensitiser (modified Buehler test)

Short term toxicity

Target / critical effect:	Nervous system / Cholinesterase inhibition
Lowest relevant oral NOAEL / NOEL:	NOAEL: 0.03 mg/kg bw (56-d-rat; LOAEL: 0.06 mg/kg bw/d) according to JMPR criteria.
Lowest relevant dermal NOAEL / NOEL:	1 mg/kg bw (21-d-rat; LOAEL: 15 mg/kg bw/d) according to JMPR criteria.
Lowest relevant inhalation NOAEL / NOEL:	1.1 mg/m^3 (90-d-rat)

Genotoxicity

Not mutagenic.

Long term toxicity and carcinogenicity

Target / critical effect:	Cholinesterase inhibition
Lowest relevant NOAEL:	oral, 2 years, rat: 2 ppm (0.1 mg/kg bw/d)
Carcinogenicity:	Negative

Reproductive toxicity

Target / critical effect - Reproduction:	Parental and pups ChE inhibition
Lowest relevant reproductive NOAEL / NOEL:	NOEL (rat) 0.1 mg/kg bw/d
Target / critical effect - Developmental toxicity:	None
Lowest relevant developmental NOAEL / NOEL:	2.5 mg/kg bw/d (highest dose treated)

Delayed neurotoxicity

Delayed neuropathy only at very high doses (3-4 times higher than the LD_{50}, hen).

Other toxicological studies

NOAEL 0.3 mg/kg bw/d from acute neurotoxicity study on rat

Developmental neurotoxicity (rat): No additional findings of concern NOAEL 1 ppm (0.085 mg/kg bw/d).

Medical data

Some Authors claim that this compound would induce a peripheral neuropathy starting a few days after severe overexposure (so called ‘intermediate syndrome‘). The clinical, pathological and functional features of these neuropathies have been extensively discussed in the literature, leading to conclude that the existence of this disease as a separate nosological entity is not yet demonstrated.

Summary

	Value	Study	Safety factor
ADI:	0.001 mg/kg bw/d	2 year rat	100
AOEL systemic:	0.001 mg/kg bw/d	2 year rat	100
ARfD (acute reference dose):	0.003 mg/kg bw/d	acute neurotoxicity study rat	100

(See Paragraph 3: Overall Conclusion)

Dermal absorption

5% (estimate from human volunteer and monkey studies and from in vivo/in vitro data)

2 Fate and behaviour in the environment

2.1 Fate and behaviour in soil

Route of degradation

Aerobic:

Mineralization after 100 days:	49% after 5 d
Non-extractable residues after 100 days:	31% after 5 d
Major metabolites above 10 % of applied active substance: name and/or code % of applied rate (range and maximum)	S-methyl phosphoramidate (M05) is the major metabolite; desamino-methamidophos (M01) is the minor one. Both metabolites in turn degraded rapidly under aerobic conditions to CO_2, the principal degradation product. M05 reaches 27% of the applied dose in 1 d (0% at 5 d)

Supplemental studies

Anaerobic:	Methamidophos degrades rapidly in soil under anaerobic conditions. S-methyl phosphoramidothioate is the major metabolite (35% at 31 d) and seems to not degrade under anaerobic conditions Non-extractable residues are 22% at 61 d.
Soil photolysis:	Photodecomposition of methamidophos on a thin layer of sandy loam soil by continuous simulated sunlight is rapid. S-methyl-phosphoramidothioate (M05) is the major photoproduct (24% at 87 hours) and desamino-methamidophos (M01) (6% at 45 hours) is the minor one. Non-extractable residues are 17% at 87 hours. Mineralisation is 33% at 87 hours. Soil pH seems to have limited effect on photolysis of methamidophos.
Remarks:	None

Rate of degradation

Laboratory studies

DT_{50}lab (20 °C, aerobic):	Methamidophos DT_{50}lab (20°C; aerobic) : ranges from 1.8 h to 6.1 d at temperature varying from 20°C to 25°C. These values normalised to 20°C (Q10=2.2) give a range from 1.8 h to 6.6 days. Mean values: 2.41 d (n=9). Median: 2.1d. M05 DT_{50}lab (20°C; aerobic): 1.9, 3.3, 4.9 hours (n=3), r^2=0.99. Mean value: 3.4 hours
DT_{90}lab (20 °C, aerobic):	Methamidophos DT_{90}lab (20°C; aerobic): ranges from 6.1 h to 6.99 d, mean value: 48.4 h (n = 4), median: 9.8 h M05 DT_{90}lab (20°C; aerobic): 6.3, 11.1, 16.1 hours (n=3), r^2=0.99. Mean value: 11.2 hours
DT_{50}lab (10 °C, aerobic):	DT_{50}lab (10°C; aerobic): evaluated with a Q10 of 2.2. It ranges from 0.2 to 14.5 d. Mean value: 5.3 d (n=9). Median: 5.3 d
DT_{50}lab (20 °C, anaerobic):	DT_{50}lab (20°C; anaerobic) : 4d
	degradation in the saturated zone: not relevant

Field studies (country or region)

DT_{50f} from soil dissipation studies:	DT_{50}f: The half-lives were estimated to be less than 2 days in the trials conducted in Germany (Monheim, Burscheid, Leichlingen) and less than one day in a trial conducted in US, California (Chualar, Fresno).
DT_{90f} from soil dissipation studies:	DT_{90}f: the maximum value has been less than 10 d.
Soil accumulation studies:	Studies not necessary since the DT_{90} field values for methamidophos are less than 10 d.
Soil residue studies:	Soil residue testing is not necessary since residues be reliably estimated from data on soil degradation (lab) and soil dissipation (field).

Remarks: e.g. effect of soil pH on degradation rate	No influence of pH on degradation rate.

Adsorption/desorption

K_f / K_{oc}:	Methamidophos The a.i. is weakly or not adsorbed to soil (n=7). K_{oc} value were obtained from 4 soils: 0.88 (clay loam) to 5.69 (high organic silty clay loam at 15°C). The K_{oc} estimated from sterilised soils from column leaching study (n=3) is 8.
K_d:	K_d: 0.029 (clay loam) to - 0.12 (high organic silty clay loam) (1/n= 0.17 to 1.28 respectively; n = 4) M05 The K_{oc} estimated from sterilised soils from column leaching study (n=3) ranges from 7 to 13 Adsorption (a.i.) decreases by increasing temperature.
pH dependence:	No

Mobility

Laboratory studies:

Column leaching:	Guidelines: US EPA, EC and SETAC Precipitation:50.8 cm Time period: 5 d Non sterile soil columns Every fifth leachate fraction of the Methamidophos columns was analyzed and yielded very low to zero amounts of a.s. Methamidophos was detected only in one leachate fraction of one of the three soil columns: 0.3% of the applied dose. K_d or K_{oc} values could not be calculated.
Aged residue leaching:	Approximately 80% of the original applied radioactivity was lost during the ageing process of 30 d. Study not appropriately designed.

Field studies:

Lysimeter/Field leaching studies:	Not available.

Remarks:	No remarks

2.2 Fate and behaviour in water

Abiotic degradation

Hydrolytic degradation:	pH 4: DT_{50} (extrapolated to 22°C) = 660 d pH 5: at 25°C, DT_{50}= 309 d
	pH 7: DT_{50} (extrapolated to 22°C) = 5 d at 25°C, DT_{50}= 27 d
	pH 9: DT_{50} (extrapolated to 22°C) = 3 d at 25°C, DT_{50}= 3 d
Major metabolites:	S-methyl phosphoramidothioate (M05) and dimethyl disulfide (M10)
Photolytic degradation:	Photolysis of methamidophos in aqueous solutions follows first-order kinetics either by continuous simulated sunlight and natural sunlight. The two half-lives differs for a factor 2.4: 37 d for simulated sunlight and 90 d for natural sunlight. It is rather likely that the degradation measured there was not caused by direct, but by indirect photoreactions.
Major metabolites:	Desamino-methamidophos (M01) and S-methyl phosphoramidothioate (M05)

Biological degradation

Readily biodegradable:	According to the water/sediment-study, convincing evidence was demonstrated that methamidophos and its metabolites are degraded to a degree of more than 70% within 28 d. Methamidophos may be regarded as "readily degradable".
Water/sediment study:	
DT_{50} water:	DT_{50} water: 4.0 d and 7.8 d
DT_{90} water:	
DT_{50} whole system:	DT_{50} whole system: 4.1 d and 5.8 d
DT_{90} whole system:	DT_{90} whole system: 13.8 d and 19.3 d
Distribution in water / sediment systems (active substance)	After an incubation time of 32 d, only 0.4% (ditch) and 1.2% (pond) of the applied a.i. was still detectable in the total systems.
Distribution in water / sediment systems (metabolites)	No major metabolites found. Maximum concentration: 7.7% of applied dose at 7 d (loamy silt)
Accumulation in water and/or sediment:	No potential for accumulation

Degradation in the saturated zone

Studies on degradation in the saturated zone were not performed because methamidophos and its degradation products are not expected to leach below the root zone.

Remarks:

No remarks.

2.3 Fate and behaviour in air

Volatility

Vapour pressure:	Test material: batch-no.: 870716ELB05 (purity 99.5%). Results: 2.3 x 10^{-5} h Pa at 20°C
Henry's law constant:	H < 1.6 x 10^{-6} Pa x m^3 x mol^{-1} (calculated).

Photolytic degradation

Direct photolysis in air:	Not required
Photochemical oxidative degradation in air DT_{50}:	Calculated half-life in air: 0.578 d Chemical lifetime in the troposphere: 0.838 d
Volatilisation:	from plant surfaces : 36% r.a. in 24 h (component not known).
	from soil : 1.9%

Remarks:	No remarks.

3 Ecotoxicology

Terrestrial Vertebrates

Acute toxicity to mammals:	Males: LD_{50} oral rat 11.8 mg/kg bw Females: LD_{50} oral rat 10.5 mg/kg bw *LD_{50} (mg as/kg bw): 79.95 rat
Acute toxicity to birds:	LD_{50} *Junco hyemalis* 8 mg/kg bw LD_{50} (mg as/kg bw) 10.54 (Bobwhite Quail)
Dietary toxicity to birds:	5 day LC_{50} Bobwhite quail 42 mg/kg diet
Reproductive toxicity to birds:	NOEL 0.29 mg /kg bw/d
Long term oral toxicity to mammals:	2 generations developmental NOEL reproduction in rat = 2.5 mg/kg bw/d

*) refined LD_{50}, based on daily dietary doses from a one day feeding study in mice (BRENDLER-SCHWAB 2001)

Aquatic Organisms

	Group	Test substance	Time-scale	Endpoint	Toxicity (mg/l)
Acute toxicity fish:	Oncorhynchus mykiss	Methamidophos techn	96h	LC_{50}	40
	Leuciscus idus melanotus	600 EC	96h	LC_{50}	112
Long term toxicity fish:	Oncorhynchus mykiss	Methamidophos techn	97 d	NOEC	2.15
Bioaccumulation fish:				Log P_{ow} -0.8	
Acute toxicity invertebrate:	Daphnia magna	Methamidophos techn	48h	EC_{50}	0.27
Chronic toxicity invertebrate:	Daphnia magna	Methamidophos techn	21d	NOEC	0.026
Acute toxicity algae:	Scenedesmus subspicatus	Methamidophos techn	96h	EC_{50} (growth inhibition)	> 178
	Scenedesmus subspicatus	600 SL	96h	EC_{50} (growth inhibition)	202
Chronic toxicity sediment dwelling organism:	No data	No data	No data	No data	No data
	Microcosm or mesocosm tests: No data available				

Honeybees

Acute oral toxicity:	No laboratory data have been provided, a cage & field study is reported, conducted on Methamidophos 720 SL at 0.56 kg a.s/ha which proved the toxicity to bees exists but rapidly decreasing (reduced bee visitation for 2-3 days and a slight higher number of bees killed than observed in water-treated plots for 1 day. The overall effect considered to be a moderately low toxicity level on honeybees).
Acute contact toxicity:	No laboratory data have been provided, a cage & field study is reported, conducted on Methamidophos 720 SL at 0.56 kg a.s/ha which proved the toxicity to bees exists but rapidly decreasing (reduced bee visitation for 2-3 days and a slight higher number of bees killed than observed in water-treated plots for 1 day. The overall effect considered to be a moderately low toxicity level on honeybees).

Other arthropod species

Species	Stage	Test substance	Endpoint	Effect
Typhlodromus pyri	protonymphs	Methamidophos SL600	LR_{50}: Extended lab	98.1 g a.s./ha
Typhlodromus pyri	protonymphs	Methamidophos SL200	LR_{50} Extended lab	127 g a.s./ha
Aphidius rhopalosiphi	adult	Methamidophos SL200	LR_{50} Extended lab	2.52 g a.s./ha
Aphidius rhopalosiphi	adult	Methamidophos SL600	LR_{50} Extended lab	1.29 g a.s./ha**
*Aphidius rhopalosiphi**	adult	Methamidophos SL200	Mortality Reproduction	no significant effects after 56 d after treatment (1400 g a.s./ha)
Crysoperla carnea	larvae	Methamidophos SL200	LR_{50} Extended lab	33.1 g as/ha
Poecilus cupreus	adult	Methamidophos SL200	LR_{50} Extended lab	795.1g a.s./ha

*Aged-residue test

**Off-field HQ values related to this end point, indicate low risk if buffer zone of 10 meters is applied.

Earthworms

Acute toxicity:	LC_{50}: 28.8 form/kg d.w. soil *Eisenia foetida* LC_{50}: 73 form/kg d.w. soil *Eisenia foetida* NOEC: 1 mg form/kg d.w. soil *Eisenia foetida*
Reproductive toxicity:	no data

Soil micro-organisms

Nitrogen mineralization:	no significant influence on the mineralization of nitrogen at 5.3 and 26.8 mg a.s./kg soil.
Carbon mineralization:	no significant influence on the mineralization of carbon at 5.3 and 26.8 mg a.s./kg soil.

APPENDIX IIIA

METHAMIDOPHOS

List of studies for which the main submitter has claimed data protection and which during the re-evaluation process were considered as essential for the evaluation with a view to Annex I inclusion.

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, B.5 Methods of analysis

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports[7] on previous use in granting national authorizations
IIIA 2.4.1 IIIA 2.4.2 IIIA 2.5.1 IIIA 2.5.2 IIIA 2.5.3 IIIA 2.6.1	Gueldner, W	2002	Determination of acidity, pH-value, viscosity, surface tension and relative viscosity of Tamaron SL 200 Blue Bayer AG, File No.: 1410505207 GLP: yes Published: no	
IIIA 2.5.1 IIIA 2.5.2 IIIA 2.5.3	Gueldner, W	2002	Determination of viscosity and surface tension of Tamaron SL 600 (article No. : 00926523) Bayer AG, File No.: MO-02-003757 GLP: yes Published: no	
IIA 4.2.2, 4.2.3 IIIA 5.2.2, 5.2.3	Sommer, H	2002	Method 00739 for the determination of residues of methamidophos and S-MATP-Na in soil and water by HPLC/MS/MS Bayer AG, File No.:00739 GLP: yes Published: no	Germany Dec 2004

[7] Entries are based on information received from the Notifier. Neither the Commission nor the Member States are responsible for the completeness or validity of this information received.

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIIA 7.7.1	Ellisor, G. K.	1998	Evaluation of foliar dislodgeable residues of Monitor on tomatoes Source: Bayer Corp., USA Bayer AG, File No.: 107246 Date: Oct. 23, 1998 GLP: yes published: no	
IIIA 7.7.1	Ellisor, G. K.	1998	Evaluation of dislodgeable foliar residues of Monitor (methamidophos) on potatoes Source: Bayer Corp., USA Bayer AG, File No.: 108415 Date: Oct. 20, 1998 GLP: yes published: no	
5.8.6/03	Fuller, B.	2000	A dermal/intravenous crossover bioavailability study of 14C-methamidophos in male Rhesus monkey Bayer AG, File No.: 109812 Date: Aug. 15, 2000 GLP: yes published: no	Germany Dec 2004
5.10.2.2	Heimann, K. G.	2002	Methamidophos - Sensitivity of animal data for humans related to cholinesterase level in brain Bayer AG, File No.: MO-02-001718 Date: Jan. 24, 2002 GLP: no published: no	Germany Dec 2004
5.10.2.2	Heimann, K. G.	2004	Methamidophos - Comparison of human and animal data in establishing the AOEL Bayer AG, File No.: MO-04-002877 Date: March 12, 2004 GLP: no published: no	Germany Dec 2004

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
5.8.6	Pallen, C.	2004	Methamidophos - 13-week oral rat study - 3-week dermal rat study - Statiastical evaluation of the relationship between the cholinesterase depression and the quantitiy of active ingredient Bayer AG, File No.: MO-04-005272 Date: 02.03.2004 GLP: no published: no	
5.8.6	Pontal, P.-G.	2004	Estimated human dermal absorption of Methamidophos Bayer AG, File No.: MO-04-005277 Date: 15.03.2004 GLP: no published: no	Germany Dec 2004
5.8.6	Sandt, J. J. M. van de	1998	In vitro percutaneous absorption of Methamidophos through human and rat skin Bayer AG, File No.: 108679 Date: 16.01.1998 GLP: yes published: no	Germany Dec 2004
5.8.6	Sangha, G. K.	2003	Position paper on the estimated human dermal absorption of Methamidophos Bayer AG, File No.: 200631 Date: 09.07.2003 GLP: no published: no	Germany Dec 2004
5.8.6/02	Selim, S.	2000	Absorption, excretion, balance and pharmacokinetics of 14C-radioactivity after single dose dermal application of two levels of 14C-labelled methamidophos from a Tamaron 600 SL formulation administered to healthy volunteers Bayer AG, File No.: BC9267 Date: Aug. 02, 2000 GLP: yes published: no	Germany Dec 2004

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
5.8.7	Sheets, L. P.	2001	Developmental neurotoxicity screen with technical grade methamidophos (Monitor) Source: Bayer Corp., USA Bayer AG, File No.: MO-01-022066 Date: Sep. 21, 2001 GLP: no published: no	
5.8.7	Sheets, L. P. Lake, S. G.	2002	A developmental neurotoxicity screening study with technical grade methamidophos (Monitor) in Wistar rats Source: Bayer Corp., USA Bayer AG, File No.: 110924 Date: Feb. 11, 2002 GLP: yes published: no	Germany Dec 2004
5.3.3.1	Sheets, L. P.; Gastner, M. E.; Hamilton, B. F.	1998	Repeated-dose 21-day dermal toxicity study with technical grade Methamidophos (Monitor) in rats Bayer AG, File No.: BC8388 Date: 28.09.1998 GLP: yes published: no	Germany Dec 2004
5.8.6 /04	Testman, R.	2000	Determination of the volatility of 14C-methamidophos from rat skin Bayer AG, File No.: BC9245 Date: Aug. 8, 2000 GLP: yes published: no	Germany Dec 2004
IIIA	Vohr, H.-W.	2002	SRA 5172 600 SL - Study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman) Bayer AG, File No.: 32023 GLP: yes published: no	Germany Dec 2004

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
5.7.1.4	Wilkinson, C. F. Wilkinson, C.	2003	An analysis of the in vivo sensitivity of animal and human cholinesterases (blood and brain) to inhibition by methamidophos Bayer AG, File No.: Date: 12.05.2003 GLP: no published: no Date of dispatch: May, 2003 Reason for submission: Data requirement (ECCO 136)	Germany Dec 2004
IIIA 7.7.1	Willard, T. R.	1998	Dissipation of dislodgeable foliar methamidophos residues from Monitor 4 treated potatoes Source: Bayer Corp., USA Bayer AG, File No.: 108559 Date: Oct. 23, 1998 GLP: yes published: no	

B.7 Residue data

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA, 6.9 (6.10 /05)	Kolbe G	2003	Acute and Chronic Dietary Risk-Methamidophos Date: 28.03.2003 BCS AG, File No.: MO-04-006179 published: No	Germany Dec 2004

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
Annex IIA 7.1.3.1; Annex IIIA 9.1.2.1	Babczinski, P., Sommer, H	2002	Leaching behaviour of methamidophos (Tamaron) and methamidophos-S-methyl-phosphoramidothioate (M05) in three soil columns Bayer AG, File No.: MR-079/02 GLP: yes published: no	Germany Dec 2004
Annex IIA 7.2.1.3.1	Leicht, W. Borchers, H.	2001	Biodegradability of methamidophos. Comments concerning the environmental Risk Phrase R53 Bayer AG, File No.: REG01-0015 GLP: no published: no	Germany Dec 2004
Annex IIIA 9.2.1	Schaefer, H.	2002	Predicted environmental concentration of methamidophos and its metabolite O-desmethyl-methamidophos in ground water recharge based on FOCUS-PELMO - Use in potatoes and tomatoes in Northern and Southern Europe Bayer AG, File No.: MR-195/02 GLP: no published: no	Germany Dec 2004
Annex IIIA 9.2.1	Schaefer, H.	2000	Predicted environmental concentration of methamidophos in groundwater recharge based on FOCUS-PELMO. Use in potatoes Bayer AG, File No.: MR-542/00 GLP: no published: no	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
Annex IIA 7.1.1; Annex IIIA 9.1.1	Stupp, H.-P.	2002	Degradation of O-desmethyl-methamidophos in three soils under aerobic conditions Bayer AG, File No.: MR-065/02 GLP: yes published: no	Germany Dec 2004

B.9 Ecotoxicology

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Anon.	2003	Methamidophos Risk assessment for non-target arthropods Bayer AG, File No.: MO-03-007838 Date: 14.05.2003 GLP: no published: no Date of dispatch: May, 2003 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	
IIA 8.1; IIIA 10.1	Barfknecht, R.	2001	Methamidophos (techn. ai): 1-day-dietary test for adult bobwhite quail (Colinus virginianus) Bayer AG, File No.: BAR/LC012 GLP: yes published: no Reason for submission: Open point	Germany Dec 2004
Annex IIIA, points 10.1 and 10. 3	Barfknecht, R.	2003	Attractiveness of potato fields for herbivorous mammals and birds, field monitoring in Nordrhein-Westfalen, Germany Bayer AG, File No.: BAR/FS 015 Date: 28.04.2003 GLP: yes published: no Date of dispatch: May 13th, 2003 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	Germany Dec 2004

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
Annex IIIA, points 10.1 and 10.3	Barfknecht, R.	2003	Attractiveness of tomato fields for herbivorous mammals and birds, field monitoring in Lombardia Bayer AG, File No.: BAR/FS 014 Date: 19.05.2003 GLP: yes published: no Date of dispatch: May, 2003 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	
IIIA 10.3	Brendler-Schwaab, S.	2001	SRA 5172 VL60 (Methamidophos) - 1-day-dietary LC50 for mice followed by a 13-days recovery period Bayer AG, File No.: T 2071130 Date: Dec. 18, 2001 GLP: yes published: no Reason for submission: Open point	Germany Dec 2004
IIA 8.6	Leicht, W. Schnorbach, H.-J.	2002	Methamidophos: Results from phytotoxicity screening experiments Bayer AG, File No.: REG02-0043 Date: May 23, 2002 GLP: no published: no Data protection Date of dispatch: May 24, 2002 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.4)	Germany Dec 2004

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Maus, C.	2002	Acute effects of Metamidophos SL 200 on adult carabid beetles (Poecilus cupreus) under extended laboratory test conditions Bayer AG, File No.: Maus/PC 014 Date: 23.01.2003 GLP: yes published: no Date of dispatch: May 13th, 2003 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	Germany Dec 2004
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U	2002	Acute dose-response toxicity of Methamidophos SL 200 (blue) to the green lacewing Chrysoperla carnea (Steph.) under extended laboratory conditions Bayer AG, File No.: 021048041 Date: 03.12.2002 GLP: yes published: no Date of dispatch: December 20, 2002 Reason for submission: Data requiremen t (SANCO/4340/2000 rev. 0-2, No. 3.3)	Germany Dec 2004
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Acute dose-response toxicity of Methamidophos SL 200 (blue) to predatory mite Typhlodromus pyri Scheuten under extended laboratory conditions Bayer AG, File No.: 021048038 Date: 17.10.2002 GLP: yes published: no Date of dispatch: December 20, 2002 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	Germany Dec 2004

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Acute dose-response toxicity of Methamidophos SL 600 to predatory mite Typhlodromus pyri Scheuten under extended laboratory conditions Bayer AG, File No.: 021048040 Date: 16.10.2002 GLP: yes published: no Date of dispatch: December 20, 2002 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	Germany Dec 2004
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Acute dose-response toxicity of Methamidophos SL 200 (blue) to the cereal aphid parasitoid Aphidius rhopalosiphi (Destefani-Perez) under extended laboratory conditions (flat-leaf design) Bayer AG, File No.: 021048037 Date: 06.12.2002 GLP: yes published: no Date of dispatch: May 13th, 2003 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	Germany Dec 2004
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Toxicity of Methamidophos SL 200 (blue) to the cereal aphid parasotoid Aphidius rhopalosiphi (Destefani-Perez) under extended laboratory conditions (aged-residue test, on apple leaves in the flat-leaf design) Bayer AG, File No.: 021048042 Date: 06.12.2002 GLP: yes published: no Date of dispatch: December 20, 2002 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	Germany Dec 2004

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Acute dose-response toxicity of Methamidophos SL 600 to the cereal aphid parasitoid Aphidius rhopalosiphi (Destefani-Perez) under extended laboratory conditions (flat-leaf design) Bayer AG, File No.: 021048039 Date: 28.11.2002 GLP: yes published: no Date of dispatch: December 20, 2002 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	Germany Dec 2004
Annex IIIA, points 10.1 and 10.3	Wolf, C.	2003	Risk assessment birds and mammals for methamidophos - safe uses for Annex I Listing Bayer AG, File No.: Date: 20.05.2003 GLP: no published: no Date of dispatch: May, 2003 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)	
Annex IIA 8.1	Wolf, C.	2004	Position paper on risk assessment birds and mammals for methamidophos - safe uses for Annex I listing Bayer AG, File No.: MO-04-003298 Date: 15.03.2004 GLP: no published: no	
Annex IIA 8.6	Wolf, C.; Fuelling, O.; Giessing, B.; Kuppels, U.; Neumann, C.; Nuesslein, F.; Wilkens, S.	2003	Magnitude and time course of residues in arthropods as potential food items for terrestrial vertebrates - first data from field experiments Bayer AG, File No.: MO-04-002852 Date: 31.12.2003 GLP: no published: yes	

APPENDIX IIIB

METHAMIDOPHOS

List of studies which were submitted during the evaluation process and were not cited in the draft assessment report:

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, B.5 Methods of analysis

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIA 4.2.5 IIIA 5.2.5	Frenzel, T. Sochor, H Speer, K Uihlein, M	2000	Rapid multimethod for verification and determination of toxic pesticides in whole blood by means of capillary GC-MS Source: Hoechst Schering AgrEvo, Frankfurt, Germany Bayer AG, File No.: 00561 Date: 01.07.2000 GLP: no Published: yes
IIIA 2.4.1 IIIA 2.4.2 IIIA 2.5.1 IIIA 2.5.2 IIIA 2.5.3 IIIA 2.6.1	Gueldner, W	2002	Determination of acidity, pH-value, viscosity, surface tension and relative viscosity of Tamaron SL 200 Blue Bayer AG, File No.: 1410505207 Date: 15.02.2002 GLP: yes Published: no
IIIA 2.5.1 IIIA 2.5.2 IIIA 2.5.3	Gueldner, W	2002	Determination of viscosity and surface tension of Tamaron SL 600 (article No. : 00926523) Bayer AG, File No.: MO-02-003757 Date: 20.02.2002 GLP: yes Published: no

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA 4.2.1 IIIA 5.2.1	Linkerhaegner, M. Pelz, S.	2002	Enforcement method 0086/M042 for the determination of residues of methamidophos in materials of plant origin-validation of DFG method S19 (extended revision) Bayer AG, File No.: 00086/M042 Date: 15.05.2002 GLP. yes Published: no
IIA 4.2.2 IIIA 5.2.2	Pelz, S. Linkerhaegner, M	2002	Enforcement method 00086/M043 for the determination of residue of methamidophos in soil-Validation of DFG method S19 (extended revision) Bayer AG, File No.: 00086/M043 Date: 17.05.2002 GLP: yes Published: no
IIA 4.2.1 IIIA 5.2.1	Pelz, S. Weber, H	2002	Enforcement method 00086/M041 for the determination of residues of methamidophos in material of animal origin-validation of DFG method S19 (extended revision) Bayer AG, File No.: 00086/M041 Date: 22.05.2002 GLP: yes Published: no
IIA 4.2.1 IIIA 5.2.1	Preu, M	2002	Independent laboratory validation of enforcement method 00086/M041 (DFG method S19, extended version) for the determination of residues of methamidophos in/on matrices of animal origin by GC-FPD and GC-NPD Bayer Ag, File No.: MR-170/02 Date: 17.05.2002 GLP: yes Published: no
IIA 4.2.1 IIIA 5.2.1	Preu, M.	2002	Independent laboratory validation of enforcement method 00086/M042 DFG S19, (extended version) for determination of residues of methamidophos in/on matrices of plant origin by GC-FPD and GC-NPD Bayer AG, File No.: MR-179/02 Date: 17.05.2002 GLP: yes Published: no

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA 4.2.3 IIIA 5.2.3	Sommer, H	2002	Enforcement method for the determination of methamidophos in drinking and surface water Bayer AG, File No.: MR-051/02 Date: 22.05.2002 GLP: yes Published: no
IIA 4.2.2, 4.2.3 IIIA 5.2.2, 5.2.3	Sommer, H	2002	Method 00739 for the determination of residues of methamidophos and S-MATP-Na in soil and water by HPLC/MS/MS Bayer AG, File No.:00739 Date: 18.02.2002 GLP: yes Published: no
IIA 4.2.4 IIIA 5.2.4	Stupp, H.P.	2002	Confirmation method for the determination of methamidophos in air by HPLC-MS/MS Bayer AG, File No.: 00284C Date: 25.02.2002 GLP: yes Published: no

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
5.8.6	Anon.	1970	Einzelwerte zu Bericht Nr.2165 vom 29. Juni 1970 BAY 71628 – Subchronische toxikologische Untersuchungen an Ratten (Fuetterungsversuch ueber 3 Monate) Bayer AG, File No.: Date: 29.06.1970 GLP: no published: no
5.8.6	Bagos, A. C.; Beatty, P. W.	1991	The percutaneous absorption of Methamidophos (SX-1757) in male rats Bayer AG, File No.: BC5365 Date: 08.01.1991 GLP: yes published: no
5.3.3	Christenson, W. R.	1991	Technical grade Methamidophos (Monitor): An eight-week subchronic cholinesterase study in Fischer 344 rats Bayer AG, File No.: BC5582 Date: 19.03.1991 GLP: yes published: no
IIIIA 7.7.1	Ellisor, G. K.	1998	Evaluation of foliar dislodgeable residues of Monitor on tomatoes Source: Bayer Corp., USA Bayer AG, File No.: 107246 Date: Oct. 23, 1998 GLP: yes published: no
IIIIA 7.7.1	Ellisor, G. K.	1998	Evaluation of dislodgeable foliar residues of Monitor (methamidophos) on potatoes Source: Bayer Corp., USA Bayer AG, File No.: 108415 Date: Oct. 20, 1998 GLP: yes published: no

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
5.8.6/03	Fuller, B.	2000	A dermal/intravenous crossover bioavailability study of 14C-methamidophos in male Rhesus monkey Bayer AG, File No.: 109812 Date: Aug. 15, 2000 GLP: yes published: no
5.10.2.2	Heimann, K. G.	2004	Methamidophos - Comparison of human and animal data in establishing the AOEL Bayer AG, File No.: MO-04-002877 Date: March 12, 2004 GLP: no published: no
5.10.2.2	Heimann, K. G.	2002	Methamidophos - Sensitivity of animal data for humans related to cholinesterase level in brain Bayer AG, File No.: MO-02-017961 Date: Nov. 28, 2002 GLP: no published: no
5.10.2.2	Heimann, K. G.	2002	Methamidophos - Sensitivity of animal data for humans related to cholinesterase level in brain Bayer AG, File No.: MO-02-001718 Date: Jan. 24, 2002 GLP: no published: no
5.3.3	Loeser, E.	1970	BAY 71628 - Subchronic toxicological studies on rats (three-month feeding experiment) Bayer AG, File No.: 2165 Date: 29.06.1970 GLP: no published: no
5.8.6	Pallen, C.	2004	Methamidophos - 13-week oral rat study - 3-week dermal rat study - Statiastical evaluation of the relationship between the cholinesterase depression and the quantitiy of active ingredient Bayer AG, File No.: MO-04-005272 Date: 02.03.2004 GLP: no published: no

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
5.8.6	Pontal, P.-G.	2004	Estimated human dermal absorption of Methamidophos Bayer AG, File No.: MO-04-005277 Date: 15.03.2004 GLP: no published: no
5.8.6	Sandt, J. J. M. van de	1998	In vitro percutaneous absorption of Methamidophos through human and rat skin Bayer AG, File No.: 108679 Date: 16.01.1998 GLP: yes published: no
5.8.6	Sangha, G. K.	2003	Position paper on the estimated human dermal absorption of Methamidophos Bayer AG, File No.: 200631 Date: 09.07.2003 GLP: no published: no
5.8.6/02	Selim, S.	2000	Absorption, excretion, balance and pharmacokinetics of 14C radioactivity after single dose dermal application of one dose lever of 14C labeled Methamidophos from a Tamaron 600 SL formulation administered to healthy volunteers Bayer AG, File No.: BC9267 Date: 02.08.2000 GLP: yes published: no
5.8.7	Sheets, L. P.	2001	Developmental neurotoxicity screen with technical grade methamidophos (Monitor) Source: Bayer Corp., USA Bayer AG, File No.: MO-01-022066 Date: Sep. 21, 2001 GLP: no published: no

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
5.8.7	Sheets, L. P. Lake, S. G.	2002	A developmental neurotoxicity screening study with technical grade methamidophos (Monitor) in Wistar rats Source: Bayer Corp., USA Bayer AG, File No.: 110924 Date: Feb. 11, 2002 GLP: yes published: no
5.3.3.1	Sheets, L. P.; Gastner, M. E.; Hamilton, B. F.	1998	Repeated-dose 21-day dermal toxicity study with technical grade Methamidophos (Monitor) in rats Bayer AG, File No.: BC8388 Date: 28.09.1998 GLP: yes published: no
5.8.6 /04	Testman, R.	2000	Determination of the volatility of 14C-methamidophos from rat skin Bayer AG, File No.: BC9245 Date: Aug. 8, 2000 GLP: yes published: no
IIIA 7.7.1	W. Maasfeld	2003	POSITION PAPER: Operator, Bystander and Worker Exposure to Methamidophos - Bayer Cropscience AG development Bayer AG, File No.: MO-03-009868 Date: 28.07.2003 GLP: no published: no
IIIA	Vohr, H.-W.	2002	SRA 5172 600 SL - Study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman) Bayer AG, File No.: 32023 GLP: yes published: no

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
5.7.1.4	Wilkinson, C. F. Wilkinson, C.	2003	An analysis of the in vivo sensitivity of animal and human cholinesterases (blood and brain) to inhibition by methamidophos Bayer AG, File No.: Date: 12.05.2003 GLP: no published: no Date of dispatch: May, 2003 Reason for submission: Data requirement (ECCO 136)
IIIA 7.7.1	Willard, T. R.	1998	Dissipation of dislodgeable foliar methamidophos residues from Monitor 4 treated potatoes Source: Bayer Corp., USA Bayer AG, File No.: 108559 Date: Oct. 23, 1998 GLP: yes published: no

B.7 Residue data

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
6.8.2/03	Dikshit, A. K. Handa, S. K. Verma, S.	1986	Residues of methamidophos and effect of washing and cooking in cauliflower, cabbage and Indian colza Source: Indian Journal of Agricultural Sciences Volume: 56; Issue: 9; Pages: 661 - 666 Bayer AG, File No.: MO-01-016614 Date: 30.09.1986 GLP: no published: yes
6.8.2/04	Jacob, S. Verma, S.	1990	Decontamination of cauliflower and okra treated with methamidophos Source: Plant Protection Bulletin Volume: 42; Issue: 1 - 2; Pages: 17 - 19 Bayer AG, File No.: MO-01-016607 Date: 31.12.1990 GLP: no published: yes
IIA, 6.9 *(6.10 /05)*	Kolbe G	2003	Acute and Chronic Dietary Risk Methamidophos Bayer AG, File No.: MO-04-006179 Date: 28.03.2003 GLP: no
6.8.8/02	Lenz, C. A.	1994	Monitor 4 - Magnitude of the residue on potato processed commodities Source: Miles, USA Bayer AG, File No.: 101235 Date: 15.07.1994 GLP: yes published: no
6.8.8/01	Misra, S. S. Agrawal, H. O. Dikshit, A. K.	1990	Persistence of residues of some organophosphate insecticides in potato in north western hills Source: Indian Journal of Plant Protection Volume: 18; Pages: 77 - 80 Bayer AG, File No.: MO-01-016620 Date: 31.01.1990 GLP: no published: yes

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
6.8.2/02	Ong, K. H. Ch'ng, A. L. Chua, G. C. Chua, S. B. Ng, B. B. Luk, S. C.	1988	Dissipation of pesticide residues from leafy vegetable, cai xin (Brassica Chinensis) Source: Singapore Journal of Primary Industries Volume: 16; Issue: 1; Pages: 41 - 59 Bayer AG, File No.: MO-01-016622 Date: 31.12.1988 GLP: no published: yes
6.8.2/05	Tsai, C.-F. Chou, S.-S. Shyu, Y.	1997	Removal of methamidophos and carbofuran residue in broccoli during freezing processing Source: Journal of Food and Drug Analysis Volume: 5; Issue: 3; Pages: 217 - 224 Bayer AG, File No.: MO-01-016625 Date: 31.12.1997 GLP: no published: yes

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
Annex IIA 7.1.3.1; Annex IIIA 9.1.2.1	Babczinski, P., Sommer, H.	2002	Leaching behaviour of methamidophos (Tamaron) and methamidophos-S-methyl-phosphoramidothioate (M05) in three soil columns Bayer AG, File No.: MR-079/02 Date: 14.03.2002 GLP: yes published: no
Annex IIA 7.2.1.2	Hellpointner, E.	2001	Position paper explaining the degradation of methamidophos and the possible photolysis of the degradation product reported in study MR88830 (MO-99-000181) File No.: MO-01-022001 Date: 03.09.2001 GLP: no published: no
Annex IIA 7.2.1.3.1	Leicht, W. Borchers, H.	2001	Biodegradability of methamidophos. Comments concerning the environmental Risk Phrase R53 Bayer AG, File No.: REG01-0015 Date: 01.03.2001 GLP: no published: no
Annex IIIA 9.2.1	Schaefer, H	2002	Predicted environmental concentration of methamidophos and its metabolite O-desmethyl-methamidophos in ground water recharge based on FOCUS-PELMO - Use in potatoes and tomatoes in Northern and Southern Europe Bayer AG, File No.: MR-195/02 Date: 14.05.2002 GLP: no published: no
Annex IIIA 9.2.1	Schaefer, H.	2000	Predicted environmental concentration of methamidophos in groundwater recharge based on FOCUS-PELMO. Use in potatoes Bayer AG, File No.: MR-542/00 Date: 20.11.2000 GLP: no published: no

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
Annex IIA 7.1.1; Annex IIIA 9.1.1	Stupp, H.-P.	2002	Degradation of O-desmethyl-methamidophos in three soils under aerobic conditions Bayer AG, File No.: MR-065/02 Date: 19.03.2002 GLP: yes published: no

B.9 Ecotoxicology

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Anon.	2003	Methamidophos Risk assessment for non-target arthropods Bayer AG, File No.: MO-03-007838 Date: 14.05.2003 GLP: no published: no
IIA 8.1; IIIA 10.1	Barfknecht, R.	2001	Methamidophos (techn. ai): 1-day-dietary test for adult bobwhite quail (Colinus virginianus) Bayer AG, File No.: BAR/LC012 Date: Nov. 20, 2001 GLP: yes published: no
Annex IIIA, points 10.1 and 10. 3	Barfknecht, R.	2003	Attractiveness of potato fields for herbivorous mammals and birds, field monitoring in Nordrhein-Westfalen, Germany Bayer AG, File No.: BAR/FS 015 Date: 28.04.2003 GLP: yes published: no Date of dispatch: May 13th, 2003 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)
Annex IIIA, points 10.1 and 10.3	Barfknecht, R.	2003	Attractiveness of tomato fields for herbivorous mammals and birds, field monitoring in Lombardia Bayer AG, File No.: BAR/FS 014 Date: 19.05.2003 GLP: yes published: no Date of dispatch: May, 2003 Reason for submission: Data requirement (SANCO/4340/2000 rev. 0-2, No. 3.3)

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIIA 10.3	Brendler-Schwaab, S.	2001	SRA 5172 VL60 (Methamidophos) - 1-day-dietary LC50 for mice followed by a 13-days recovery period Bayer AG, File No.: T 2071130 Date: Dec. 18, 2001 GLP: yes published: no
Annex IIA 8.1	Davies, N.B.	1977	Prey selection and social behaviour in wagtails (Aves: Motacillidae) Bayer AG, File No.: MO-04-002844 Date: 31.12.1977 GLP: no published: yes
Annex IIA 8.1	Dittberner, H.; Dittberner, W.	1984	Die Schafstelze - Motacilla flava Bayer AG, File No.: MO-04-002838 Date: 31.12.1984 GLP: no published: yes
Annex IIA 8.1	Glutz von Blotzheim, U. N.; Bauer, K. M.	1985	Handbuch der Voegel Mitteleuropas - Band 10/II - Schafstelze (Motacilla flava) Bayer AG, File No.: MO-04-002849 Date: 31.12.1985 GLP: no published: no
IIA 8.6	Leicht, W. Schnorbach, H.-J.	2002	Methamidophos: Results from phytotoxicity screening experiments Bayer AG, File No.: REG02-0043 Date: May 23, 2002 GLP: no published: no
Annex IIA 8.1	Mason, C.F.; Macdonald, S.M.	1999	Influence of landscape and land-use on the distribution of breeding birds in farmland in eastern England Bayer AG, File No.: MO-03-015847 Date: 11.08.1999 GLP: no published: yes

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Maus, C.	2002	Acute effects of Metamidophos SL 200 on adult carabid beetles (Poecilus cupreus) under extended laboratory test conditions Bayer AG, File No.: Maus/PC 014 Date: 23.01.2003 GLP: yes published: no
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Acute dose-response toxicity of Methamidophos SL 200 (blue) to predatory mite Typhlodromus pyri Scheuten under extended laboratory conditions Bayer AG, File No.: 021048038 Date: 17.10.2002 GLP: yes published: no
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Acute dose-response toxicity of Methamidophos SL 600 to predatory mite Typhlodromus pyri Scheuten under extended laboratory conditions Bayer AG, File No.: 021048040 Date: 16.10.2002 GLP: yes published: no
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Acute dose-response toxicity of Methamidophos SL 200 (blue) to the cereal aphid parasitoid Aphidius rhopalosiphi (Destefani-Perez) under extended laboratory conditions (flat-leaf design) Bayer AG, File No.: 021048037 Date: 06.12.2002 GLP: yes published: no
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Toxicity of Methamidophos SL 200 (blue) to the cereal aphid parasotoid Aphidius rhopalosiphi (Destefani-Perez) under extended laboratory conditions (aged-residue test, on apple leaves in the flat-leaf design) Bayer AG, File No.: 021048042 Date: 06.12.2002 GLP: yes published: no

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Acute dose-response toxicity of Methamidophos SL 600 to the cereal aphid parasitoid Aphidius rhopalosiphi (Destefani-Perez) under extended laboratory conditions (flat-leaf design) Bayer AG, File No.: 021048039 Date: 28.11.2002 GLP: yes published: no
Annex IIA, point 8.3.2 Annex IIIA, point 10.5	Roehlig, U.	2002	Acute dose-response toxicity of Methamidophos SL 200 (blue) to the green lacewing Chrysoperla carnea (Steph.) under extended laboratory conditions Bayer AG, File No.: 021048041 Date: 03.12.2002 GLP: yes published: no
Annex IIA 8.1	Stromborg, K. L.	1985	Reproduction of bobwhites fed different dietary concentrations of an organophosphate insecticide, methamidophos Bayer AG, File No.: MO-03-005495 Date: 09.11.1985 GLP: no published: yes
Annex IIA 8.1 Annex IIIA, points 10.1 and 10.3	Wolf, C.	2004	Position paper on risk assessment birds and mammals for methamidophos - safe uses for Annex I listing Bayer AG, File No.: MO-04-003298 Date: 15.03.2004 GLP: no published: no
Annex IIIA, points 10.1 and 10.3	Wolf, C.	2003	Risk assessment birds and mammals for methamidophos - safe uses for Annex I Listing Bayer AG, File No.: MO-03-007875 Date: 30.06.2003 GLP: no published: no

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
Annex IIA 8.6	Wolf, C.; Fuelling, O.; Giessing, B.; Kuppels, U.; Neumann, C.; Nuesslein, F.; Wilkens, S.	2003	Magnitude and time course of residues in arthropods as potential food items for terrestrial vertebrates - first data from field experiments Bayer AG, File No.: MO-04-002852 Date: 31.12.2003 GLP: no published: yes

APPENDIX IV

List of uses supported by available data

Methamidophos

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Potatoes	NMS	Tamaron SL 200 Tamaron SL 600	F	coleoptera	SL	19.5% 600 g/L	High volume spraying	at infestation[8]	1	n.a.	0.12	400	0.48	14	
Potatoes	NMS	Tamaron SL 200 Tamaron SL 600	F	aphidina	SL	19.5% 600 g/L	High volume spraying	at infestation[9]	3	10	0.12	400	0.48	14	
Potatoes	SMS	Tamaron SL 200 Tamaron SL 600	F	aleurodidae, aphidina, lepidoptera, thysanoptera	SL	19.5% 600 g/L	High volume spraying	at infestation	1-3	10	0.09	350-560	0.32-0.5	21	

[8] In Germany typical applications are performed at growth stage (BBCH) 51-59 (end of June)
[9] In Germany the first application is usually performed at growth stage (BBCH) 31 - 39 (begin or middle of June)

Remarks:

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

COMMISSION DIRECTIVE 2006/131/EC

of 11 December 2006

amending Council Directive 91/414/EEC to include methamidophos as an active substance

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market ([1]), and in particular Article 6(1) thereof,

Whereas:

(1) Commission Regulation (EEC) No 3600/92 of 11 December 1992 laying down the detailed rules for the implementation of the first stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC concerning the placing of plant protection products on the market ([2]), establishes a list of active substances to be assessed, with a view to their possible inclusion in Annex I to Directive 91/414/EEC. That list includes methamidophos.

(2) For methamidophos the effects on human health and the environment have been assessed in accordance with the provisions laid down in Regulation (EEC) No 3600/92 for a range of uses proposed by the notifier. By Commission Regulation (EC) No 933/94 of 27 April 1994 laying down the active substances of plant protection products and designating the Rapporteur Member State for the implementation of Commission Regulation (EEC) No 3600/92 ([3]), Italy was designated as Rapporteur Member State. Italy submitted on 30 July 1999 the relevant assessment report and recommendations to the Commission in accordance with Article 7(1)(c) of Regulation (EEC) No 3600/92.

(3) The assessment report has been reviewed by the Member States and the Commission within the Standing Committee on the Food Chain and Animal Health.

(4) The review of methamidophos revealed a number of open questions which were addressed by the Scientific Panel on Plant health, Plant protection products and their Residues (PPR) of the European Food Safety Authority (EFSA). The Scientific Panel was asked to define a value for the degree of dermal adsorption scientifically based on the different results of the studies submitted by the notifier to be used in the assessment of human risk arising from the dermal route of exposure. Moreover, the Scientific Panel was asked to review the estimates of avoidance, time spent foraging in treated areas and proportion of contaminated diet obtained in treated areas, and advise on their implications for estimates of acute, short and long term exposure of birds and mammals to the insecticide methamidophos. In its opinion on the first question the PPR Panel concluded ([4]) that, on the basis of the available data the best estimated dermal adsorption of the diluted preparation is considered to be about 5 %. On the second question, the PPR Panel concentrated its assessment on two species considered by the notifier and Rapporteur Member State, yellow wagtail and wood mouse, as they make substantial use of the crops supported for methamidophos. The PPR Panel disagreed ([5]) with the values proposed by the notifier and the Rapporteur Member State as regards the proportion of contaminated diet set for yellow wagtails and the estimates used in dietary composition for yellow wagtails and wood mouse. The PPR Panel noted that these values would underestimate acute exposure of individual animals. The PPR Panel developed an alternative approach for assessing the potential role of avoidance. The mechanisms involved are complex but it appears possible that both yellow wagtail and wood mouse might feed quickly enough for mortality to occur in field conditions. The PPR Panel identified several options for laboratory or field studies, which could be considered to assess these risks with more certainty.

(5) Articles 5(4) and 6(1) of Directive 91/414/EEC provide that inclusion of a substance in Annex I may be subject to restrictions and conditions. In this case, restrictions on the inclusion period and on the authorised crops are deemed necessary. The original measures presented to the Standing Committee on the Food Chain and Animal

([1]) OJ L 230, 19.8.1991, p. 1. Directive as last amended by Commission Directive 2006/85/EC (OJ L 293, 24.10.2006, p. 3).
([2]) OJ L 366, 15.12.1992, p. 10. Regulation as last amended by Regulation (EC) No 2266/2000 (OJ L 259, 13.10.2000, p. 10).
([3]) OJ L 107, 28.4.1994, p. 8. Regulation as last amended by Regulation (EC) No 2230/95 (OJ L 225, 22.9.1995, p. 1).
([4]) Opinion of the Scientific Panel on Plant Health, Plant Protection Products and their Residues on a request from the Commission related to the evaluation of methamidophos in toxicology in the context of Council Directive 91/414/EEC (*The EFSA Journal* (2004), 95, 1 to 15). Adopted on 14 September 2004.
([5]) Opinion of the Scientific Panel on Plant Health, Plant Protection Products and their Residues on a request from the Commission related to the evaluation of methamidophos in ecotoxicology in the context of Council Directive 91/414/EEC (*The EFSA Journal* (2004), 144, 1 to 50). Adopted on 14 December 2004.

Health, proposed the restriction of the inclusion period to seven years, so that Member States would give priority to reviewing plant protection products already on the market containing methamidophos. In order to avoid discrepancies in the high level of protection sought, the inclusion in Annex I to Directive 91/414/EEC was intended to be limited to the uses of methamidophos that have been actually assessed within the Community evaluation and for which the proposed uses were considered to comply with the conditions of Directive 91/414/EEC. This implies that other uses, which were not or only partially covered by this assessment, had first to be subject to a complete assessment, before their inclusion in Annex I of Directive 91/414/EEC could be considered. Finally, due to the hazardous nature of methamidophos, it was considered necessary to provide for a minimum harmonisation at Community level of certain risk mitigation measures that were to be applied by Member States when granting authorisations.

(6) Under the procedures laid down by Directive 91/414/EEC, the approval of active substances, including the definition of risk management measures, is decided by the Commission. Member States bear the responsibility for the implementation, application and control of the measures intended to mitigate the risks generated by plant protection products. Concerns expressed by several Member States reflect their judgment that additional restrictions are necessary to reduce the risk to a level that can be considered acceptable and consistent with the high level of protection that is sought within the Community. At present, it is a question of risk management to set the adequate level of safety and protection for the continued production, commercialisation and use of methamidophos.

(7) As a consequence of the above, the Commission re-examined its position. In order to correctly reflect the high level of protection of human and animal health and a sustainable environment sought in the Community, it considered appropriate, in addition to the principles set out in Recital 5, to further reduce the period of inclusion to 18 months instead of seven years. This further reduces any risk by ensuring a priority re-assessment of this substance.

(8) It may be expected that plant protection products containing methamidophos satisfy the requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC, with regard to the uses which were examined and detailed in the Commission review report and providing that the necessary risk mitigation measures are applied.

(9) Without prejudice to the conclusion that plant protection products containing methamidophos may be expected to satisfy the requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC, it is appropriate to obtain further information on certain specific points. Article 6(1) of Directive 91/414/EEC provides that inclusion of a substance in Annex I may be subject to conditions. Therefore, it is appropriate to require that methamidophos should be subjected to further testing for confirmation of the risk assessment for birds and mammals and that such studies should be presented by the notifiers. In addition, Member States should require authorisation holders to provide information on the use of methamidophos including any information on incidences on operator health.

(10) As with all substances included in Annex I to Directive 91/414/EEC, the status of methamidophos could be reviewed under Article 5(5) of that Directive in the light of any new data becoming available. Equally, the fact that the inclusion of this substance in Annex I expires on a particular date does not prevent the inclusion being renewed according to the procedures laid down in the Directive.

(11) The experience gained from previous inclusions in Annex I to Directive 91/414/EEC of active substances assessed in the framework of Regulation (EEC) No 3600/92 has shown that difficulties can arise in interpreting the duties of holders of existing authorisations in relation to access to data. In order to avoid further difficulties it therefore appears necessary to clarify the duties of the Member States, especially the duty to verify that the holder of an authorisation demonstrates access to a dossier satisfying the requirements of Annex II to that Directive. However, this clarification does not impose any new obligations on Member States or holders of authorisations compared to the directives which have been adopted until now amending Annex I.

(12) A reasonable period should be allowed to elapse before an active substance is included in Annex I in order to permit Member States and the interested parties to prepare themselves to meet the new requirements which will result from the inclusion.

(13) Without prejudice to the obligations defined by Directive 91/414/EEC as a consequence of including an active substance in Annex I, Member States should be allowed a period of six months after inclusion to review existing authorisations of plant protection products containing methamidophos to ensure that the requirements laid down by Directive 91/414/EEC, in particular in its Article 13 and the relevant conditions set out in Annex I, are satisfied. Member States should vary, replace or withdraw, as appropriate, existing authorisations. in accordance with the provisions of Directive 91/414/EEC. By derogation from the above deadline, a longer period should be provided for the submission and assessment of the complete Annex III dossier of each plant protection product for each intended use in accordance with the uniform principles laid down in Directive 91/414/EEC. Given the hazardous properties of methamidophos, the period for Member States to verify whether the plant protection products, which contain methamidophos as the only active substance or in combination with other authorised active substances, comply with the provisions of Annex VI should not exceed 18 months.

(14) It is therefore appropriate to amend Directive 91/414/EEC accordingly.

(15) The measures provided for in this Directive are not in accordance with the opinion delivered by the Standing Committee on the Food Chain and Animal Health. The Commission therefore submitted to the Council a proposal relating to these measures. On the expiry of the period laid down in the second subparagraph of Article 19(2) of Directive 91/414/EEC, the Council had neither adopted the proposed implementing act nor indicated its opposition to the proposal for implementing measures and it is accordingly for the Commission to adopt these measures,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Annex I to Directive 91/414/EEC is amended as set out in the Annex to this Directive.

Article 2

Member States shall adopt and publish by 30 June 2007 at the latest the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith communicate to the Commission the text of those provisions and a correlation table between those provisions and this Directive.

They shall apply those provisions from 1 July 2007.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

Article 3

1. Member States shall in accordance with Directive 91/414/EEC, where necessary, amend or withdraw existing authorisations for plant protection products containing methamidophos as an active substance by 30 June 2007.

By that date they shall in particular verify that the conditions in Annex I to that Directive relating to methamidophos are met, with the exception of those identified in part B of the entry concerning that active substance, and that the holder of the authorisation has, or has access to, a dossier satisfying the requirements of Annex II to that Directive in accordance with the conditions of Article 13.

2. By derogation from paragraph 1, for each authorised plant protection product containing methamidophos, Member States shall re-evaluate the product in accordance with the uniform principles provided for in Annex VI to Directive 91/414/EEC, on the basis of a dossier satisfying the requirements of Annex III to that Directive and taking into account part B of the entry in Annex I to that Directive concerning methamidophos. On the basis of that evaluation, they shall determine whether the product satisfies the conditions set out in Article 4(1)(b), (c), (d) and (e) of Directive 91/414/EEC.

Following that determination Member States shall for products containing methamidophos, where necessary amend or withdraw the authorisation by 30 June 2008.

Article 4

This Directive shall enter into force on 1 January 2007.

Article 5

This Directive is addressed to the Member States.

Done at Brussels, 11 December 2006.

For the Commission

Markos KYPRIANOU

Member of the Commission

ANNEX

The following entries shall be added at the end of the table in Annex I to Directive 91/414/EEC:

No	Common name, identification numbers	IUPAC name	Purity (1)	Entry into force	Expiration of inclusion	Specific provisions
'145	Methamidophos CAS No 10265-92-6 CIPAC No 355	O,S-dimethyl phosphoramidothioate	≥ 680 g/kg	1 January 2007	30 June 2008	PART A Only use as insecticide on potato may be authorised. The following conditions of use must be respected: — At rates not exceeding 0,5 kg active substance per hectare per application, — Maximum 3 applications per season. The following uses must not be authorised: — air application, — knapsack and all hand-held applications, neither by amateur nor by professional users, — home gardening. Member States shall ensure that all appropriate risk mitigation measures are applied. Particular attention must be paid to the protection of: — birds and mammals. Conditions of authorisation shall include risk mitigation measures, such as a judicious timing of the application and the selection of those formulations which, as a result of their physical presentation or the presence of agents that ensure an adequate avoidance, minimise the exposure of the concerned species, — aquatic organisms and non-target arthropods. An appropriate distance must be kept between treated areas and surface water bodies as well as margins of the crop. This distance may depend on the application or not of drift reducing techniques, — operators, who must wear suitable protective clothing, in particular gloves, coveralls, rubber boots and respiratory protective devices during mixing-loading and gloves, coveralls, rubber boots and face protection or safety glasses during application and cleaning of equipment. The above measures must be applied, unless the exposure to the substance is adequately precluded by the design and construction of the equipment itself or by the mounting of specific protective components on such equipment.

No	Common name, identification numbers	IUPAC name	Purity (1)	Entry into force	Expiration of inclusion	Specific provisions
						PART B For the implementation of the uniform principles of Annex VI, the conclusions of the review report on methamidophos, and in particular Appendices I and II thereof, shall be taken into account. Member States must ensure that the authorisation holders report at the latest on 31 December of each year on any reported effect on operator health. Member States may require that elements, such as sales data and a survey of use patterns, are provided so that a realistic picture of the use conditions and the possible toxicological impact of methamidophos can be obtained. Member States shall request the submission of further studies to confirm the risk assessment for birds and mammals. They shall ensure that the notifiers at whose request methamidophos has been included in this Annex provide such studies to the Commission within 1 year from the entry into force of this Directive.'

(1) Further details on identity and specification of active substance are provided in the review report.