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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use (CVMP)

European public MRL assessment report (EPMAR)

Phoxim (extension to bovine species and harmonisation of MRLs)

On 11 December 2012 the European Commission adopted a Regulation[1] establishing maximum residue limits for phoxim in all food producing species except fin fish, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Maximum residue limits had previously been established for phoxim in ovine, porcine and chicken species. On 13 December 2010 Bayer Animal Health GmbH submitted to the European Medicines Agency an application for the extension of MRLs for phoxim to bovine species and, at the same time, the modification of the existing MRLs to produce a harmonised set of MRLs in all species for which MRLs are established.

Phoxim is intended for use in bovine species in the control of mites, lice and other ectoparasites. For wash and spray treatment of cattle, the intended concentrations of phoxim solutions are 250 to 1000 mg phoxim/litre. In pigs, sheep and poultry phoxim is also used for the control of ectoparasites.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended, on 8 March 2012, the modification of the existing maximum residue limits for phoxim, the extension of the MRLs to bovine species, and extrapolation of the MRLs to all food producing species except fin fish.

Subsequently the Commission recommended, on 25 October 2012, that a single set of maximum residue limits be established in all food producing species except fin fish. This recommendation was confirmed on 15 November 2012 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 11 December 2012.

[1] Commission Implementing Regulation (EU) No 1186/2012,O.J. L338/20, of 12.12.2012

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Phoxim
Therapeutic class:	Antiparasitic agents / Agents against ectoparasites
Procedure number:	EU/10/183/BAY
Applicant:	Bayer Animal Health GmbH
Target species:	Cattle, sheep, pigs, chickens
Intended therapeutic indication:	control of mites, lice and other ectoparasites
Route(s) of administration:	topical

1. Introduction

Phoxim (CAS 14816-18-3) is an organophosphorous insecticide currently used in veterinary medicine for the control of mites, lice and other ectoparasites in pigs, sheep and chickens. Phoxim is administered topically either as a wash, spray or pour-on. For wash and spray treatment of pigs, a 500 to 1000 mg phoxim/l solution should be applied at approximate volumes of 0.5 to 1 litre per animal, to be repeated after 14 days. For pour-on treatment of pigs, a solution of 75 mg phoxim/ml is applied topically at a dose of 30 mg phoxim/kg bw, to be repeated after 14 days. For wash and spray treatment of sheep, a 500 to 1000 mg phoxim/l solution should be applied at appropriate volumes of 2 to 3 l/animal, to be repeated after 14 days. For dip treatment sheep are dipped for at least 30 seconds in a solution containing 500 mg phoxim/l. In laying hens, phoxim is intended for treatment and control of the red mite. Cages are sprayed with 25 ml of a solution containing 2 g phoxim/l. The laying hens stay in the cages during treatment and will be exposed to phoxim.

Phoxim had a very limited use in plant protection in the European Union. Authorisations for plant protection products containing phoxim were withdrawn from the market in 2007 (Commission Decision 2007/442/EC).

Phoxim was previously evaluated by the Committee for Medicinal Products for Veterinary Use (CVMP) for use in pigs, sheep and chickens. The CVMP established an ADI of 0.00375 mg/kg bw (i.e. 0.225 mg/person).

Currently phoxim is included in Commission Regulation (EU) No 37/2010 of 22 December 2009 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Phoxim	Phoxim	Ovine	50 µg/kg 400 µg/kg 50 µg/kg	Muscle Fat Kidney	Not for use in animals from which milk is produced for human consumption	Antiparasitic agents/ Agents against ectoparasites
		Porcine	20 µg/kg 700 µg/kg 20 µg/kg 20 µg/kg	Muscle Skin and fat Liver Kidney		
		Chicken	25 µg/kg 550 µg/kg 50 µg/kg 30 µg/kg 60 µg/kg	Muscle Skin and fat Liver Kidney Eggs		

On 13 December 2010 Bayer Animal Health GmbH submitted an application for the extension of MRLs for phoxim to bovine species and, at the same time, the modification of the existing MRLs to produce a harmonised set of MRLs in all species for which MRLs are established.

The proposed indication for bovine species is the control of mites, lice and other ectoparasites. For wash and spray treatment of cattle, the intended concentrations of phoxim solutions are 250 to 1000 mg phoxim/litre.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of phoxim and established an ADI of 0.00375 mg/kg bw (i.e. 0.225 mg/person) based on the NOEL of 0.375 mg/kg bw/day from effects on the liver and reduction of acetylcholinisterase activity in the brain observed in a 2-year feeding study in dogs. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this application.

2.2. Residues assessment

Previous CVMP evaluations of phoxim have included residues data in pigs, sheep and chickens. The data provided for each of these species, as well as the data provided for bovine species, are summarised in the sections below.

2.2.1. Pharmacokinetics in target species

Pigs

Pharmacokinetic studies were performed following oral and dermal administration to pigs. After oral administration at a dose of 5 mg/kg bw, phoxim was rapidly and completely absorbed from the gastro-

intestinal tract, with peak plasma levels occurring within 2 hours. Phoxim was rapidly distributed to the tissues and organs, with highest concentrations found in fat, kidney and liver. Phoxim was quickly eliminated, mainly via the urine (more than 80%) and to a lesser extent in faeces (less than 12.5%). Following a single pour-on treatment at a dose of 100 mg/kg bw, the dermal bioavailability of phoxim was low (1.2 to 2.9%).

The metabolism of phoxim was studied in a number of species including pigs. Apart from some qualitative and quantitative differences in metabolism between different animal species, it can be concluded that the main degradation steps in pigs (and rats and rabbits) involved hydrolysis of the phosphor ester bond and de-alkylation, rendering (conjugates of) cyanobenzaldoxime (further detoxified to hippuric acid in rats and pigs) and desethyl (PO-) phoxim, respectively.

Radiolabelled phoxim was administered orally in gelatin capsules to two pigs at a single dose of 5 mg/kg bw. The animals were slaughtered 24 and 72 hours after administration (only one animal per time point). Highest radioactive residues were found at 24 hours after administration: 1320 µg equivalents/kg in fat, 600 µg equivalents/kg in liver, 350 µg equivalents/kg in kidney and 50 µg equivalents/kg in muscle. At 72 hours, tissue concentrations were approximately half these values. In the tissues only phoxim and cyanobenzaldoxime could be identified. Quantification was only possible in fat (limit of quantification not given), in which phoxim represented 90% of radioactivity. Phoxim was also identified in loin and muscle. Cyanobenzaldoxime was found in muscle, loin and liver.

In a radiolabel study in seven pigs, phoxim was dermally administered as a pour-on at a dose of 100 mg/kg bw. The dermal bioavailability was 1.2 to 2.9%.

Sheep

Six sheep received single topical applications with ^{14}C-phoxim in N-butanol as vehicle at a dose of 25 mg/kg bw. Four additional sheep received the same test substance in N-methylpyrrolidone intravenously at a single dose of 1 mg/kg bw, in order to provide tissue and excreta samples for metabolite profiling in the event of (excessively) low levels of radioactivity being absorbed after topical application. The animals were slaughtered in groups of 1 male and 1 female at 4 and 8 hours after intravenous injection or 7, 21 and 28 days after topical administration. At slaughter, samples of the application site (topically treated sheep), blood, liver, kidneys, muscle (fore and hind quarter), abdominal fat (omental and perirenal mixed) and subcutaneous fat (remote from the application site) were taken for analysis. Excreta were collected up to 7 days after application, and blood samples were taken before administration and at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after administration, where applicable, for all animals and then at 24 hour intervals up to slaughter. All samples were analysed for total radioactivity, and if possible, further analysed for the parent compound and metabolites. The analytical techniques involved were LSC, TLC, HPLC (radiodetection and UV detection), LC-MS, and LC-MS/MS.

The following values for pharmacokinetic parameters for radioactivity concentrations in plasma following a single topical application to sheep were obtained: Cmax (µg equivalents/g) 0.084 (n=3); Tmax (hours) 192 (median, n=3); AUC0-168h (µg equivalents.h/g) 11.8 (n=3); AUC0-504h 31.4 (n=2); AUC0-672h 30.4 (n=1); k (hours) 0.0029 (n=2); t½ (hours) 243.2 (n=2). At seven days the total recovery of radioactivity was in the range of 64 to 85%. The majority of the radioactivity was

associated with the applications site (42 to 64% of the dose). Excretion via urine accounted for 7 to 11.5% of the dose and via faeces for 0.7 to 2.6% of the dose at 7 days. Phoxim was not detected in urine. The main metabolite in urine was cyanoxim and its glucuronide and sulphate conjugates, together accounting for approximately 68% of the radioactivity in urine. The metabolite profile in urine following intravenous injection was similar.

The highest concentrations of total radioactive residues were found in liver (ranging from 1603 µg phoxim equivalents/kg at day 7 to 775 µg/kg at day 28) and fat (ranging from 2071 µg phoxim equivalents/kg at day 7 in abdominal fat to 542 µg/kg at day 28 in subcutaneous fat). Residues were less abundant in muscle and kidney; at day 28 the levels were down to 115 µg phoxim equivalents/kg in kidney and to 59 µg/kg in muscle. The radioactivity in fat was readily extractable, but in kidney and in muscle only approximately 30% was extractable, whereas the radioactivity in liver was hardly extractable (less than 5%, although at 4 hours after the intravenous dose 40% of the radioactivity in liver was extractable). The vast majority of the radioactivity in fat consisted of the parent compound. Other extractable metabolites in fat were not identified.

Chickens

Six female laying hens (Hisex, more than 26 weeks of age, bodyweight 1.4 to 1.9 kg) were dermally treated with ^{14}C-phoxim diluted in butan-1-ol and in propan-2-ol to a final concentration of 200 mg active ingredient/ml, with a specific activity of 5.31 mCi/mmol (196.5 kBq/mg). The substance was applied at the base of the feathers on the back. Five of these animals were given a dose of 11.3 to 12.4 mg/kg bw, and one animal received a dose of 19.5 mg/kg bw. Another 12 hens were given the ^{14}C-phoxim (in capsules) at doses in the range of 4.66 to 5.79 mg/kg bw to allow metabolic profiling. The birds given the dermal treatment were slaughtered 12 days after application. Of the orally treated birds, six were slaughtered at 6 hours after application and the remaining 6 at 7 days after application.

Twelve days after dermal treatment, the highest mean concentrations of total radioactive residues were found in skin + fat from the application site (1460 µg phoxim equivalents/kg). Mean concentrations of total radioactive residues in other tissues (expressed as µg phoxim equivalents/kg) were: 270 µg/kg in kidney, 188 µg/kg in skin plus fat remote from the application site, 85 µg/kg in liver, and 2.9 to 16 µg/kg in muscle. The mean concentrations of the parent compound at 12 days after dermal treatment were: 99 µg/kg in skin + fat remote from the application site, 8.7 µg/kg in liver, and from non-detectable to 4.7 µg/kg in muscle. The concentration of phoxim was not determined in kidneys but in an additional cold residue study using the same design, the mean concentrations of phoxim in kidney was less than 2.4 µg/kg. The composition of residues was investigated in excreta, in skin and fat taken 12 days after dermal treatment, and in edible tissue (except kidney) taken 6 hours after oral treatment. All other edible tissues (including eggs) were stated to have residue concentrations that were too low for this purpose. From the data it can be concluded that the main route of metabolism is hydrolysis to z-cyanoxim and further conjugation to cyanoxim sulphate. This profile is similar to that proposed for rats, pigs and sheep, although the glucuronide conjugate of z-cyanoxim and hippuric acid were also significant metabolites in the urine and tissues of these species.

In eggs, the concentration of total radioactive residues reached a maximum of 69 µg phoxim equivalents/kg at 8 days after dermal treatment and gradually declined thereafter. The highest concentration of the parent compound, phoxim, (29 µg/kg) was also found at this time point.

Cattle

After oral administration, phoxim is rapidly and (nearly) completely absorbed in cattle, as can be concluded from the level of excretion of total phoxim-residues via urine within 24 hours (demonstrated in a non-GLP compliant study in a single cow). The same pattern was also observed in pigs and sheep.

In a non-GLP compliant study in which two cows were sprayed twice with phoxim (solution of 500 or 1000 mg/l, treatments separated by 6-8 days), the highest residue levels were found in fat tissue (0.35±0.04 mg/kg after 13 days; 0.02±0.00 mg/kg after 28 days). Residue levels of phoxim in muscle, kidney and liver were below the limit of detection (less than 0.01 mg/kg). This is in line with the distribution observed in the other species (sheep, pigs, chicken), where fat appears to be the tissue with the highest levels of marker residue phoxim.

In the oral administration study mentioned above, the excretion of phoxim was fast with 76% of the dose being excreted within 24 hours following administration. The main excretion route of phoxim (metabolites) was via urine (73% of the dose after 144 hours), and to a lesser extent via faeces (13% after 144 hours). This is in line with the other species previously assessed. The major (radioactive) metabolite found in cattle urine was hippuric acid. The main degradation step for phoxim is hydrolysis of the phosphor ester bond, rendering (conjugates of) cyanoxim (also called cyanobenzaldoxim).

It can be concluded that the metabolism and excretion of phoxim in cattle appears to be similar to that of previously assessed species, especially pigs and sheep.

2.2.1. Residue depletion studies

Pigs

In a GLP residue study, the commercial pour-on product was applied at the recommended dose (30 mg/kg bw) along the dorsal backline of twenty animals. Treatment was repeated after 14 days. The animals were slaughtered (n=4/group) at 7, 14, 21, 28 and 35 days following the second application. Phoxim concentrations were determined by high pressure liquid chromatography (HPLC) in samples of liver, kidney, muscle and abdominal fat, as well as in edible tissues at the site of application (skin, muscle and back fat). The limit of quantification was 10 µg/kg. Residues were only detectable in samples of fat and skin, with no differences between concentrations in abdominal fat and back fat. In fat the mean residue concentrations declined from 502 µg/kg at 7 days, via 220 µg/kg at 14 days, 121 µg/kg at 21 days, 86 µg/kg at 28 days, to 23 µg/kg at 35 days. The mean phoxim concentrations in skin were somewhat lower, declining from 346 µg/kg at 7 days, via 107 µg/kg at 14 days, 49 µg/kg at 21 days, 23 µg/kg at 28 days, to 11 µg/kg at 35 days.

A total of two limited residue studies in pigs following two spray treatments (interval 7 to 8 days) with a 50% emulsifying concentrate formulation with a concentration of 500 or 1000 mg phoxim/l were provided. Animals were slaughtered (n=2/group) at 14 and 28 days following spraying with 1000 mg/l, and at (n=3/group) 7 and 14 days following spraying with 500 mg/l. After the 1000 mg/l application,

residues were found in fat (without skin) only (40 and 50 µg/kg at 14 days and 0.13 and lower than 10 µg/kg at 28 days). After the 500 mg/l application only residues in fat (without skin) were studied, revealing no detectable levels of phoxim in any of the samples.

Another limited tissue residue study in pigs was provided following pour-on at the recommended dose. Phoxim was detectable in fat tissue only, the highest value of 130 µg/kg was observed 14 days after treatment.

Sheep

Depletion of residues was studied in 10 male and 10 female Suffolk sheep (bodyweight 40.5 to 51 kg, approximately 15 months of age, sheared 4 weeks before treatment, mean wool length 15 mm at treatment) dipped in an aqueous solution of phoxim that was prepared from the commercial formulation at a final nominal phoxim concentration of 500 mg per litre. Groups of 2 males and 2 females were slaughtered at 7, 21, 28, 35, and 49 days after dipping. Samples of liver, kidney, muscle (mixed sample of fore and hind quarter), and fat (subcutaneous fat, and a mixed sample of omental and perirenal fat) were taken. All samples were analysed for phoxim concentrations using an HPLC-UV technique which was the same as the proposed routine analytical method with validated limits of quantification of 200 µg/kg for fat and 25 µg/kg for all other tissues.

High levels (1532 µg/kg at 7 days) were found in fat, in particular in subcutaneous fat, in which phoxim was detectable up to the last time point of 49 days (66 µg/kg). Phoxim concentrations in muscle and kidneys were much lower (189 µg/kg, respectively 35.3 µg/kg at day 7), being only detectable up to 21 (kidney) and 28 (muscle) days. In liver samples, phoxim was not detectable at all.

Chickens

Depletion of residues was studied in 28 female Hisex hens (bodyweight 1332 to 2028 g). The hens were dermally treated with phoxim, using a 2 g phoxim/l formulation. The formulation was sprayed within a distance of about 10 cm between the spray nozzle and the hen. Each hen received a spray volume of about 10 ml, equivalent to approximately 20 mg phoxim per hen. The treatment was repeated after 7 days. Groups of four birds were slaughtered at seven and 14 days after the second treatment. The remaining birds (n=20) were slaughtered at 21 days after the second treatment. The number of eggs examined at each time point ranged from 9 to 23.

The concentrations of phoxim were determined in liver, muscle, skin and fat, and in eggs, using the proposed routine analytical HPLC-UV method. Residues in kidneys were not investigated. Highest residues were found in skin and fat ranging from 538 to 1496 µg/kg at 7 days after the second administration, declining to concentrations ranging from 398 to 579 µg/kg at 14 days and from 95.5 to 536 at 21 days. Lower levels were found in muscle, ranging from 7.77 to 23.5 µg/kg at 7 days, from 3.68 to 8.79 at 14 days, and from non-detectable to 9.73 at 21 days. Phoxim could not be detected in liver at any time point.

The concentration of phoxim in eggs reached a maximum of 12.3 µg/kg at 10 days after the second treatment, and declined gradually to 5.3 µg/kg at 20 days after second treatment. It was noted that although these were detectable concentrations, they were below the limit of quantification, which was set at 30 µg/kg, the lowest validation level used for eggs.

Cattle

Depletion of residues was studied in a GLP-compliant study in 16 cows (female, bodyweight: 297-397 kg, strain not specified) administered 7.5 mg phoxim/kg bw (i.e. 7.5 ml 0.1% spray/kg bw). Groups of 4 animals were slaughtered at 8, 16, 23 and 37 days after administration. Samples of liver, kidney, muscle (filet + back) and fat (perirenal + subcutaneous) were taken. All samples were analysed for phoxim concentrations using an HPLC-MS/MS technique which was the same as the proposed routine analytical method with validated limits of quantification of 50 µg/kg for fat and 10 µg/kg for all other tissues. Highest residues were found in fat ranging from 210 to 639 µg/kg for perirenal fat and 144 to 462 µg/kg for subcutaneous fat at 8 days after administration, declining to respectively 176 to 220 µg/kg and 166 to 297 µg/kg at 16 days, less than 50 to 146 µg/kg and 78 to 109 µg/kg at 23 days and below the limit of quantification to 95 µg/kg and below the limit of quantification to 97 µg/kg at 37 days. Lower levels were found in kidney, ranging from 13 to 58 µg/kg at 8 days, 13 to 40 µg/kg at 16 days, 14 to 22 µg/kg at 23 days and below the limit of quantification at 37 days. In muscle, phoxim was only detectable at 8 days after administration, with levels ranging from below limit of quantification to respectively 30 µg/kg for filet and 21 µg/kg for back. Phoxim could not be detected in liver at any time point.

Selection of marker residue and target tissues

Based on the results of the studies provided, the parent compound, phoxim was identified as the most suitable marker residue in pigs, sheep and chickens.

In pigs, phoxim accounted for 90% of the total residues in fat. Due to low concentrations of phoxim in muscle, liver and kidney in this species, no ratio of marker to total residues could be established in these tissues. However, it was noted that total residues in liver, kidney and muscle were at least 0.5 times less, 0.25 times less and 0.04 times less than in fat.

In sheep the highest concentrations of total radioactive residues were present in liver and fat, with lower levels present in muscle and kidney. Radioactivity in fat was present largely as parent compound. The ratio of marker to total residues was established as 0.75 for fat, 0.5 for muscle and 0.1 for kidney. No ratio of marker to total residues could be established for liver as parent compound was not seen at any time point. However, total residues in liver were approximately 1.5 times higher than in fat.

After topical treatment of hens, high concentrations of phoxim were found in skin + fat, but much lower concentrations were found in muscle, and no phoxim was detected in liver or kidney. Ratios of marker to total residues were established as 0.551 for skin + fat, 0.178 for muscle, 0.120 for liver, 0.01 for kidney, and 0.32 for eggs,

No radiolabelled residue depletion study was submitted for cattle, therefore no data on the ratio of marker to total residues in this species are availabe. However, metabolism data are available for at least one monogastric, one ruminant and one poultry species, and based on these data it is not expected that the metabolic profile for cattle will significantly differ from that seen in the other species assessed. Metabolism profiles of rats, pigs, sheep and chicken have been shown to be similar, with the main degradation step for phoxim is hydrolysis of the phosphor ester bond, rendering (conjugates of)

cyanoxim (also called cyanobenzaldoxim), which is further detoxified in pigs and sheep to hippuric acid. Also in cattle the presence of hippuric acid in the urine suggests that phoxim is metabolized by processes similar to those observed in sheep.

As the metabolism of phoxim has been seen to be similar in all species studies and as the residue depletion study in cattle confirmed the presence of phoxim in cattle tissues, phoxim is also considered to be the most suitable marker for monitoring of residues in cattle tissues. In the absence of radiolabelled data in cattle, and in light of the similarity in the metabolism of phoxim seen in all studied species, the marker to total residues established for sheep (i.e. 0.75 for fat, 0.50 for muscle and 0.1 for kidney; total residues in liver are approximately 1.5 times higher than in fat) can be adopted for cattle.

2.2.2. Monitoring or exposure data

No relevant data other than that described elsewhere in this report and in previously published CVMP Summary Reports/EPMARs are available.

2.2.3. Analytical method for monitoring of residues

In the MRL evaluation of phoxim for use in pigs an HPLC-UV method was accepted for routine residue monitoring. The limits of quantification were 350 µg/kg for skin plus fat and 10 µg/kg for liver, kidney and muscle.

In the MRL evaluation of phoxim for use in sheep an HPLC-UV method with limits of quantification of 200 µg/kg for fat and 25 µg/kg for other tissues was accepted for routine monitoring of residues.

An HPLC-UV method was also accepted for the monitoring of residues of phoxim in chicken fat, muscle liver and eggs. The limits of quantification were 200 µg/kg for skin + fat, 25 µg/kg for liver, 10 µg/kg for muscle, and 30 µg/kg for eggs. For chicken kidney an LC-MS/MS method with a limit of quantification for kidney was 25 µg/kg was accepted.

For cattle, an HPLC method with MS/MS detection has been proposed for monitoring of residues of phoxim in tissues. The reported limits of quantification are 50 µg/kg for fat and 10 µg/kg for all other tissues. The method is well described and validated according to the requirements of Volume 8 of The rules governining medicinal products in the European Union. The analytical method has been reviewed by the relevant European Reference Laboratory, which confirmed the suitability of the method for monitoring of residues.

The validated analytical methods available for chicken, pigs, sheep and cattle are not identical. However, it has been demonstrated that the proposed analytical method for cattle tissues is also applicable for sheep, pigs and chicken tissues. The relevant European Reference Laboratory has reviewed the method and confirmed its suitability for monitoring of residues in all of the above species. Therefore this method can be considered appropriate for residue control purposes in all food producing species, except fin fish.

2.2.4. Findings of EU or international scientific bodies

Phoxim was evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1999 and, based on an ADI of 0-4 µg/kg bw, temporary MRLs were established for cattle, sheep, goats and pigs at values of 50 µg/kg for muscle, liver and kidney, 400 µg/kg for fat and 10 µg/kg for cows' milk.

In 2002 the temporary MRLs for sheep, goats and pigs became final, and in 2004 the temporary MRLs for cattle tissues and cows' milk were withdrawn. No MRLs were established for chickens and eggs.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing

Microbiological effects are not expected for this type of substance and therefore no data were required.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

Phoxim had a very limited use as a pesiticide in plant protection in the European Union and its use has been discontinued. Authorisations for plant protection products containing phoxim were withdrawn in 2007 (Commission Decision 2007/442/EC). Consequently, no consideration of residues arising as a result of pesticide use is necessary.

3.3 Elaboration of MRLs

The available data (including the data provided for cattle) indicate that phoxim is the appropriate marker residue in all species. The metabolism and clearance process of phoxim is conserved across species. Phoxim is mainly excreted in the form of metabolites by the renal route and undergoes extensive hepatic metabolism. The distribution profile of phoxim is conserved between major species. After a topical application, unchanged phoxim distributes into the fatty compartment of the treated animal, and to a much lesser extent in kidney, liver and muscle. That the pharmacokinetic behaviour of phoxim is similar in different species is further reflected by the fact that similar MRL values have previously been established for ovine species, porcine species and chickens. Having now considered the available data further, it is concluded that the MRL values established for these three species could be harmonised and the MRLs established for chicken were accepted as appropriate values to apply also to pigs and sheep.

The Committee noted that while the data provided for cattle would, on their own, not be sufficient to allow the establishment of MRLs in this species, given the totality of the available data on phoxim residues in different species, the data provided for cattle can be used to support a proposal to extend the harmonised MRLs to this species also.

Therefore the following harmonised MRLs can be recommended for bovine, ovine and porcine species as well as chickens and eggs:

- Muscle: 25 µg/kg
- Fat: 550 µg/kg
- Liver: 50 µg/kg
- Kidney: 30 µg/kg
- Eggs: 60 µg/kg

As no data on residues in milk were provided, an MRL cannot be established in this food commodity and as a consequence the use of the substance in lactating animals cannot be authorised.

Calculation of theoretical daily intake of residues

Detailed calculation of theoretical daily intake of residues from cattle tissues based on the proposed MRLs for cattle and the established MRLs for eggs:

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product (µg)
Muscle	0.30	25	0.5	15.0
Fat	0.05	550	0.75	36.7
Liver	0.10	50	n.a.*	110.0**
Kidney	0.05	30	0.1	15
Milk	1.50	Not for us in animals from which milk is produced for human consumption		
Eggs	0.10	60	0.32	18.75
Total				195.45
%ADI				87

* phoxim was not detected in liver of sheep or cattle as it is extensively metabolised in this tissue
** estimated intake: total residues in liver are expected to approximately 1.5 times higher than in fat.

Based on the harmonised MRLs proposed, and taking into account the estimated total residues in liver which are approximately 1.5 times higher than in fat, the daily intake resulting from ingestion of cattle tissues would represent approximately 87% of the ADI. The proposed MRLs keep exposure within the ADI, and roughly reflect the tissue distribution in all species studied.

However, the worst case maximum daily intake of residues would result from ingestion of chicken tissues and eggs, which would result in an intake of total residues amounting to 222.4 µg, representing 98% of the ADI. It is noted that this leaves only a small portion of the ADI available for possible future uses.

There is no need to consider possible ingestion of residues resulting from use of phoxim in plant protection products as authorisations for such products were withdrawn in the EU in 2007.

The MRLs proposed differ from the MRLs established by Codex for sheep, goat and pigs. Harmonisation with the Codex MRLs was considered, however, based on the information available for poultry (chickens), for which no Codex MRLs exist, it is concluded that the extrapolation of the Codex MRLs to poultry would result in a maximum theoretical intake of 115% of the ADI (including intake from egg consumption). Therefore, the CVMP concludes that harmonisation of the Codex MRLs is not possible in view of the intake of residues from chicken tissues plus eggs, leading to an exposure in excess of the ADI.

Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of extrapolating the maximum residue limits recommended for phoxim in bovine, ovine, porcine and chicken (including eggs) to other species/food commodities.

Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

Animal species / food commodity	Extrapolation possible (yes / no)	Justification
All food producing species, except fin fish	Yes	Maximum residue limits are established or proposed for ovine, porcine, chicken and bovine species. Considering that specific residue data confirm a similar exposure of the consumer to residues from cattle, pig, sheep and chicken tissues, it can be assumed that the exposure assessment and ergo the risk characterisation on the basis of same MRLs for further species beyond these animal classes would be similar. Therefore extrapolation to all food producing species except fin fish can be recommended. An analytical method for the monitoring of phoxim residues in several animal species is available and is considered applicable to other species.
Fin fish	No	Metabolism is generally less complicated in fish than in mammals and birds, and given that the marker residue is the parent compound, in principle the same marker residue could be acceptable for fin fish. However, no information on the applicability of the analytical method to fish was available Overall, extrapolation of MRLs to fin fish is not recommended. Moreover, because phoxim is toxic to aquatic organisms and fish in particular, this substance is considered to be unsuitable for use in fish species.
Milk	No	No data are available that would allow conclusions to be drawn on the appropriate marker residue or marker to total residues ratio to use in milk. Milk is consumed on a regular basis and in large quantities and consequently data on residues in this commodity are considered necessary in order to quantify the possible impact on consumer safety of exposure to residues. No analytical method for monitoring of residues in milk was available for evaluation.
Honey	No	Residue depletion in honey does not occur through metabolism and consequently conclusions drawn from data in other food products cannot be extrapolated to honey. Honey specific data are required in order to allow adequate evaluation of the risk to consumer safety posed by residues in honey. No data are available to demonstrate that the analytical method used for monitoring of residues in other animals species/tissues is applicable for monitoring of residues in honey.

3.3. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- the toxicological ADI of 3.75 µg/kg bw (i.e. 225 µg/person) was established as the overall ADI for phoxim,
- the parent compound phoxim is considered to be the most suitable marker residue for all tissues and all species in which MRLs are recommended,
- the metabolism and residue distribution of phoxim is similar in all species studied, covering ruminants, monogastrics, and poultry,
- the ratio of marker to total residues in chicken was 0.551 for skin and fat, 0.178 for muscle, 0.120 for liver, 0.01 for kidney and 0.32 for eggs,
- the ratio of marker to total residues in sheep was 0.75 for fat, 0.50 for muscle and 0.1 for kidney. As phoxim is extensively metabolised in liver no ratio of marker to total residues ratio could be established in this tissue; total residues in liver are approximately 1.5 times higher than in fat,
- the ratio of marker to total residues in sheep can be retained for cattle,
- the ratio of marker residue to total residues in pig fat is 0.9. Due to the low concentrations in the other edible tissues of pigs the ratio of marker to total residues could not be established; total residues are at least approximately 0.5 times less, 0.25 times less and 0.04 times less in liver, kidney and muscle than in fat respectively,
- validated analytical methods for the monitoring of residues of phoxim in edible bovine, ovine, porcine and chicken tissues (and eggs) are available. Moreover, it was demonstrated that the analytical method for the monitoring of residues of phoxim in edible bovine tissue is applicable for ovine, porcine and chicken tissues and is therefore considered to be applicable for all food producing species, except fish,

the CVMP recommends the modification of the existing MRLs for phoxim, the extension of the MRLs to bovine species, the extrapolation of the MRLs to all food producing species except fin fish, and the amendment of table 1 of the Annex to Commission Regulation (EU) 37/2010, as shown in the table overleaf:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Phoxim	Phoxim	All food producing species except fin fish	25 µg/kg 550 µg/kg 50 µg/kg 30 µg/kg 60 µg/kg	Muscle Fat Liver Kidney Eggs	For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'. Not for use in animals from which milk is produced for human consumption	Antiparasitic agents/Agents against ectoparasites

The theoretical daily residue intake from poultry tissues plus eggs (worst case scenario) represents 98% of the ADI.

4. Background information on the procedure

Submission of the dossier

Steps taken for assessment of the substance

Application validated:	4 January 2011
Clock started:	5 January 2011
List of questions adopted:	4 May 2011
Consolidated response to list of questions submitted:	9 December 2011
Clock re-started:	10 December 2011
CVMP opinion adopted:	8 March 2011