Conclusion regarding the peer review of the pesticide risk assessment of the active substance ethephon

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SUMMARY

Ethephon is one of the 52 substances of the second stage of the review programme covered by Commission Regulation (EC) No 451/2000[1], as amended by Commission Regulation (EC) No 1490/2002[2]. This Regulation requires the European Food Safety Authority (EFSA) to organise a peer review of the initial evaluation, i.e. the draft assessment report (DAR), provided by the designated rapporteur Member State and to provide within one year a conclusion on the risk assessment to the EU-Commission.

The Netherlands being the designated rapporteur Member State submitted the DAR on ethephon in accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, which was received by the EFSA on 21 April 2004. Following a quality check on the DAR, the peer review was initiated on 28 June 2004 by dispatching the DAR for consultation of the Member States and the sole applicant Bayer CropScience. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and the need for additional data was agreed in an evaluation meeting on 14 December 2004. Remaining issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in June and July 2005.

A discussion of the outcome of the consultation of experts took place with representatives from the Member States on 9 February 2006 leading to the conclusions as laid down in this report.

In October 2006 an addendum on the ARfD prepared by the Netherlands was submitted to EFSA. This addendum has been discussed during the 4th round of PRAPeR expert meetings in the meeting on mammalian toxicology from 26 – 30 March 2007.

During the Standing Committee on the Food Chain and Animal Health held on 19-20 May 2008 in Brussels the ARfD for ethephon was discussed and EFSA presented a paper to describe the ARfD setting process and the supporting studies evaluated so far in the peer review. It was concluded that the RMS should prepare a new addendum to the DAR to clearly describe and summarise all the

[1] OJ No L 53, 29.02.2000, p. 25
[2] OJ No L 224, 21.08.2002, p. 25

available information for setting the ARfD. It was agreed to re-discuss the ARfD during the following round of PRAPeR expet meetings.
This second addendum on the ARfD was prepared by the Netherlands and submitted to EFSA in June 2008, which was discussed during the 11th round of PRAPeR expert meetings in the meeting of mammalian toxicology from 7 – 11 July 2008.

The outcome of the different discussions is reflected in this document, which has been amended accordingly.

The conclusion was reached on the basis of the evaluation of the representative uses as plant growth regulator comprise foliar spraying to regulate the growth of cereals (winter wheat; winter and spring barley) at an application rate of up to 480 g ethephon per hectare ("spring": 360; "winter": 480). Ethephon can be used only as plant growth regulator.
The representative formulated product for the evaluation was "Cerone" ("EXP03725B" or "AE F013382 00 SL40"), a soluble concentrate (SL), registered under different trade names in most of the Member States of the EU.

Adequate methods are available to monitor all compounds given in the respective residue definition. Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.
It should be noted that due to data gaps it was not possible for the rapporteur Member State to conclude on the comparability of the technical materials from the second applicant.

Ethephon has an oral LD_{50} of 1564 mg/kg bw, a dermal LD_{50} of 983 mg/kg bw and an inhalation LC_{50} of 3.26 mg/L. Ethephon causes severe skin irritation. Hence ethephon should be classified as 'CORROSIVE' with the associated risk phrases [R20/21/22] 'Harmful by inhalation, in contact with skin and if swallowed' and [R34] 'Causes burns'. The applicability of R43'May cause sensitisation by skin contact' was forwarded to ECB.
Ethephon is considered to be non-genotoxic and no oncogenic potential of the test substance in rats or mice was observed. There were no direct effects observed on reproductive performance or fertility. In the teratogenicity study in rabbits, no test material-related foetal variations or malformations were observed. No delayed neurotoxicity was observed in hens. The ADI, and AOEL are 0.03 mg/kg bw/d, based on the 1-year dog study and supported by human data. A safety factor of 1000 was used including an extra factor of 10 since ChE activity was not measured in the study. Originally in 2005, the ARfD was also set at 0.03 mg/kg bw based on the same 1-year dog study and safety factor of 1000, however after the submission of a new oral 28-day dog study to investigate acetylcholinesterase

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inhibition, this value was revised in 2007 and 2008, and considering both the dog and human studies, the ARfD was set at 0.05 mg/kg bw. The estimated exposure of the operator and bystanders was below the AOEL without PPE; no worker exposure is anticipated for cereals.

Following foliar application of ethephon to wheat, tomatoes and pineapple the major residue found at harvest in straw, grain, fruits and leaves, respectively, was ethephon or its metabolite 2-hydroxyethyl phosphonic acid (HEPA). Other metabolites were probably not formed. Since HEPA was present in cereals at equal levels as ethephon and was also considered toxicologically relevant, HEPA was included in the risk assessment for consumers. The experts' meeting for toxicology concluded that HEPA is even about twice more toxic than ethephon itself. However, upon receipt of late information from the applicant, the rapporteur Member State indicated during the final discussion in February 2006 that a reassessment of the potency of toxicity of HEPA might be needed.
Fed to ruminants ethephon was intensively metabolised resulting in a low total residue. Based on the properties of the molecule and additional scientific literature on metabolism of acetate it was concluded, that ethephon and 2-hydroxyethyl phosphonic acid (HEPA) are the only possible metabolic intermediates in ruminants. No significant residue levels (ethephon and HEPA) are expected when livestock (ruminants/pigs) is exposed to residue resulting from ethephon application to cereals according the evaluated cGAP, and thus no MRLs are currently proposed for food of animal origin. Studies in poultry are not triggered by the representative uses, and therefore a residue definition and MRLs are currently not necessary for poultry products.
A sufficient number of supervised residue trials are available to assess consumer exposure to the ethephon and HEPA, and to propose ethephon MRLs for wheat and barley grain as well as a conversion factor for risk assessment. The chronic and acute dietary exposure assessment for consumers based on the representative GAP on cereals indicated that none of the considered consumer subgroups was exposed above 4 % of the proposed ADI and 2% of the ARfD, respectively.

Sufficient data were available to demonstrate that ethephon is not persistent in the environment. Under aerobic conditions at 20 ºC, ethephon degraded in soil with a half-life in the range from 2.7 to 37.6 days, depending on the soil type and the pH of the soil. The major degradates are ethylene gas and the non-volatile 2-hydroxyethylphosphonic acid (the latter formed at amount < 10% AR by microbially mediated hydrolytic dehalogenation). The major routes of dissipation appear to be chemical hydrolysis and microbial degradation. Degradation in soil is slightly enhanced by irradiation. Ethephon can be characterized as having moderate to low mobility in soil. Modelling indicated that ethephon is unlikely to contaminate groundwater when used as recommended. In the field, ethephon exhibited the same characteristics (fairly rapid degradation and moderate to low mobility) as those seen in the laboratory.
Ethephon was stable to hydrolysis in acidic sterilized water, but did rapidly hydrolyze in neutral and alkaline environments. Irradiation resulted also in the hydrolysis of ethephon with ethylene as degradation product. In water and sediment, ethephon disappeared rapidly by hydrolysis in the water

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phase and only small quantities of the compound were adsorbed to the sediment. Ethephon is considered non ready biodegradable. PECsw and PECsed estimations were performed based on drift as the entry route into a static water layer 30 cm deep, a distance of 1, 5 and 10 meters.
Concentrations of ethephon in air are expected to be negligible.

The risk insectivorous birds and mammals in cereals can be regarded as low as well as the risk to birds and mammals from secondary poisoning and from consumption of contaminated drinking water.
The risk to aquatic organisms is regarded to be low without the need for risk mitigation measures.
The risk to bees and other arthropod species can be regarded as low based on the available studies.
The risk to earthworms, other soil non-target macro-organisms and soil micro-organisms can be regarded as low.
The risk to non-target plants and biological methods for sewage treatment is considered to be low.

Key words: ethephon, peer review, risk assessment, pesticide, plant growth regulator

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BACKGROUND

Commission Regulation (EC) No 451/2000 laying down the detailed rules for the implementation of the second and third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC, as amended by Commission Regulation (EC) No 1490/2002, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Ethephon is one of the 52 substances of the second stage covered by the amended Regulation (EC) No 451/2000 designating the Netherlands as rapporteur Member State.

In accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, the Netherlands submitted the report of its initial evaluation of the dossier on ethephon, hereafter referred to as the draft assessment report, to the EFSA on 21 April 2004. Following an administrative evaluation, the EFSA communicated to the rapporteur Member State some comments regarding the format and/or recommendations for editorial revisions and the rapporteur Member State submitted a revised version of the draft assessment report. In accordance with Article 8(5) of the amended Regulation (EC) No 451/2000 the revised version of the draft assessment report was distributed for consultation on 28 June 2004 to the Member States and the main applicant Bayer CropScience as identified by the rapporteur Member State. However during the evaluation process a second producer for ethephon, Phytorus S.A., submitted a dossier which was evaluated with respect to the equivalence to the technical ethephon of Bayer CropScience.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, representatives from Member States identified and agreed in an evaluation meeting on 14 December 2004 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level. A representative of the notifier attended this meeting.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in expert meetings organised on behalf of the EFSA by the EPCO-Team of the Pesticide Safety Directorate (PSD) in York, United Kingdom in June and July 2005. The reports of these meetings have been made available to the Member States electronically.

A discussion of the outcome of the consultation of experts took place with representatives from Member States on 9 February 2006 leading to the conclusions as laid down in this report.

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During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR).

In accordance with Article 8(7) of the amended Regulation (EC) No 451/2000, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received
- the resulting reporting table (rev. 1-1 of 22 December 2004)
- the consultation report

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation
- the evaluation table (rev. 2-1 of 7 March 2006)

Given the importance of the draft assessment report including its addendum (compiled version of February 2006 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.
After the discussions of the ARfD in 2007 and 2008 the peer review report and the final addendum have been amended.

By the time of the presentation of this conclusion to the EU-Commission, the rapporteur Member State has made available amended parts of the draft assessment report (Vol. 1, Vol. 2, Vol. 3 sections B1, B6-B9) which take into account mostly editorial changes. Since these revised documents still contain confidential information, the documents cannot be made publicly available. However, the information given can basically be found in the original draft assessment report together with the peer review report which both is publicly available.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Ethephon is a common name for 2-chloroethylphosphonic acid (IUPAC). At the moment there is no ISO common name for this compound.

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Ethephon belongs to the class of defoliants and ethelene releasers growth regulator such as metoxuron and 1-methylcyclopropene, respectively. Ethephon is taken up via leaves and hinder the *de novo* synthesis of fatty acids by inhibition of the enzyme Acetyl-CoA carboxylase (ACCase).

The representative formulated product for the evaluation was "Cerone" ("EXP03725B" or "AE F013382 00 SL40"), a soluble concentrate (SL), registered under different trade names in most of the Member States of the EU.

The evaluated representative uses as plant growth regulator comprise foliar spraying to regulate the growth of cereals (winter wheat; winter and spring barley) at an application rate of up to 480 g ethephon per hectare ("spring": 360; "winter": 480). Ethephon can be used only as plant growth regulator.

SPECIFIC CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

The minimum purity of ethephon as manufactured should not be less than 910 g/kg, which is identical to the minimum purity given in the FAO specification 373/TC/S/F (2000). The minimum purity of ethephon if it is used as a technical concentrate (TK) should not be less than 692 g/kg. The FAO specification gives no explicit value for the ethephon content in the TK.

According to the assessment conducted by the rapporteur Member State and summarised in the evaluation table (17261/EPCO/BVL/04 rev. 1-0; 03.11.05), the different technical materials from Bayer CropScience can be regarded as equivalent. This assessment was neither peer reviewed nor discussed in expert meetings. However, the assessment can be confirmed by EFSA from a toxicological point of view if it is assumed that the content of the impurities in the test substance used in mammalian toxicology studies were in the same order of magnitude as the specified limits. At the moment it is not possible for EFSA to confirm the assessment of the rapporteur Member State that the two technical materials can be regarded as equivalent from an ecotoxicological point of view.

According to the FAO specification, the technical material contains two impurities, which has to be regarded as relevant impurity, MEPHA[3] and 1,2-dichloroethane. The maximum content in the technical material should not be higher than 20 g/kg for MEPHA and 0.5 g/kg for 1,2-dichloroethane [373/TC/S/F (2000)]. In the case of the TK, the maximum contents of the relevant impurities should be 2% of the ethephon declared content for MEPHA and 0.04% for 1,2-dichloroethane [FAO

[3] MEPHA: 2-chloroethyl phosphonic acid, mono-2-chloroethyl ester

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specification 373/TK/S/F (2000)]. In addition, parameter with respect to the content of "material insoluble in water" and the water content are given (for details see FAO specification).
It should be noted that for the moment no information is available whether or not the content of these relevant impurities is increasing in the formulation upon storage (the fact that this information is not available was confirmed by the rapporteur Member State, after the expert meeting).
Moreover, the content of one significant impurity was above the specification proposed by the applicant. Therefore information is required to explain what happens to batches out of the specification and to clarify the specification for this impurity (AE 0764265).
Therefore, it should be noted that the specification for the technical material as a whole should be regarded as provisional for the moment.

Beside this, the assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of ethephon or the respective formulations.

The content of ethephon in the representative formulation is 480 g/L (pure).

The main data regarding the identity of ethephon and its physical and chemical properties are given in appendix 1.

Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of ethephon in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material and the relevant impurities in the formulation.
Therefore, enough data are available to ensure that quality control measurements of the plant protection product are possible.

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. ethephon in food of plant origin (cereals, only), soil, water and air. In the case that HEPA[4] is included in the residue definition for food of plant origin, it should be noted that the submitted method needs to be reviewed. The applicability of the method for the determination of HEPA was not discussed at the expert meeting. However, it seems that it would be necessary to require at least an ILV and a confirmatory method.
The methodology used is HPLC with MS/MS detection or GC with MS detection.. A multi-residue method like the Dutch MM1 or the German S19 is not applicable to due the nature of the residues.
An analytical method for food of animal origin is not required due to the fact that no residue definition is proposed (see 3.2).

[4] HEPA: 2-hydroxyethyl phosphonic acid; AE F020271

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The discussion in the expert meeting (EPCO 30, July, 2005) on identity, physical and chemical properties and analytical methods was limited to the specification of the technical materials and the technical concentrate, the equivalence of the two different Bayer CropScience sources, the shelf-life study and to the analytical methods.
It should be noted that the data gaps (batch analysis incl. validated analytical methods; purity of the starting material) identified in the DAR for the second notifier (Phytorus S.A.) are still unfulfilled.

2. Mammalian toxicology

Ethephon was discussed at EPCO expert meeting for mammalian toxicology (EPCO 28) in June and July 2005. The ARfD value was re-discussed at the PRAPeR expert's meeting on mammalian toxicology (PRAPeR 19) in March 2007 on basis of new submitted information accepted by the rapporteur Member State and referred in the addendum on ARfD (October 2006) and at the PRAPeR 54 Sub-group 2 on mammalian toxicology in July 2008 based on the addendum 2 on ARfD (June 2008).

2.1 ABSORPTION, DISTRIBUTION, EXCRETION AND METABOLISM (TOXICOKINETICS)

Ethephon is rapidly and extensively absorbed, via gastrointestinal tract in rats (78-84%, based on excretion data from urine, expired air/volatiles, cage wash, tissues and residual carcass) within 120 hours. The excretion is also rapid, mainly via urine (50-60% within 120 hours) and expired air (20% within 120 hours).) Less than 6.5% is excreted in faeces. It is widely distributed, however the amount retained in tissues and residual carcass is low (<0.5%) and the highest concentrations were found in liver, blood, kidneys, bone, spleen, lungs and heart. There was no potential for accumulation. Ethephon is extensively metabolised; the fraction containing the disodium salt of ethephon was the major component in urine and faeces, representing on average 84-87% and 47-59%, respectively, of the total radioactivity in the samples of urine and faeces which were chromatographed. Fractions other than that containing the disodium salt of ethephon individually accounted for ≤ 6.0% AR. Definitive identification of other compounds in urine besides the disodium salt of ethephon was not successful. However, new experimental procedures revealed the presence of metabolite 2-hydroxyethyl phosphonic acid (HEPA) in the kidneys and liver although at much lower levels than parent ethephon.

2.2 ACUTE TOXICITY

Ethephon needs to be classified as "harmful" based on the results of the acute oral (LD_{50} 1564 mg/kg bw), dermal (LD_{50} 983 mg/kg bw) and inhalation (LC_{50} 3.26 mg/L) toxicity studies. Ethephon should be classified as "causes burns" based on the results of the skin irritation study. No eye irritation study

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with ethephon was performed, due to the pH of 1.6. Ethephon does not have sensitising properties in a Buehler test or in an LLNA test. However, both tests were of limited value since the Buehler test was performed with far too less animals, and the experience of the LLNA test was insufficient to assess the effect of altering the pH before the test, and the influence on the results is unclear. In the Maximisation test 5 test animals revealed discrete/patchy erythema, some of them with dryness of the skin, and an additional 3 test animals showed dryness of the skin, none of these effects were observed in control animals. In the meeting, no conclusion was reached in relation to the sensitising potential of ethephon. It was decided that due to the corrosive properties of ethephon, the evidence of skin sensitization is inconclusive. It was noted that ethephon was classified as [R34] 'Causes burns', and thus classification as [R43] would not impact on the requirement for PPE, as this would be triggered by the corrosive nature of the material.

Ethephon is classified as **'CORROSIVE'** with the associated risk phrases **[R20/21/22] 'Harmful by inhalation, in contact with skin and if swallowed'** and **[R34] 'Causes burns'**. The applicability of [R43] 'May cause sensitisation by skin contact' was forwarded to ECB.

2.3 SHORT TERM TOXICITY

The short term effects of ethephon were studied in one 21-day dermal study in the rabbit, two oral 28-day studies in the rat, two oral 28-day studies in the mouse, and one 1-year study in the dog. A 28-day dietary study in female dog was presented after the decision had been taken that ethephon could be included in Annex I of Council Directive 91/414/EEC[5] to investigate only the cholinesterase inhibition that was missing in the 1-year dog study.

The main effect of ethephon is an inhibition of ChE activity in plasma and erythrocytes with female rats and mice being more sensitive than males; no effect on brain ChE activity was observed. No measurements of ChE activity in plasma, erythrocytes and brain were performed in the dermal study and in the 1-year dog study. In the dermal toxicity study no systemic effects were observed, however in the absence of measurements of ChE activity/inhibition, no NOAEL can be determined for use in risk assessments.

In the 1-year dog study ChE measurements were also not performed, and a NOAEL of 27 mg/kg bw/d was set based on decreased body, spleen and thyroid weight. However, this study appears to be the most suitable study to be used as a starting point for risk assessment, since there was some very limited and inconclusive evidence for significant inhibition of brain and erythrocyte cholinesterase activity in a 2-week range finding study with dogs. These data are very limited but do raise the possibility that dogs may be slightly more sensitive than rodents to brain cholinesterase inhibition following exposure to ethephon. In the 28-day cholinesterase inhibition study in dogs, no depression on brain cholinesterase activity were found up to the highest dose tested of 14 mg/kg bw/d. At this dose level erythrocyte acetylcholinesterase activity was decreased as well as plasma cholinesterase activity from the low dose level of 6 mg/kg bw/d and up. Since plasma cholinesterase inhibition is not

[5] OJ No L 230, 19.08.1991, p. 1-32

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considered to be an adverse effect in the absence of erythrocyte and/or brain cholinesterase inhibition, the NOAEL for cholinesterase inhibition was 6 mg/kg bw/d in this study.

Before the latter study had been submitted, the experts at the EPCO 28 meeting considered that the relevant short term NOAEL was 1000 ppm (27 mg/kg bw/d) in the dog, based on decreased body weight, and spleen and thyroid weight, keeping in mind that no data was available on ChE activity in plasma, erythrocytes and brain. On the basis of the overall updated information, the experts concluded at the PRAPeR 54 (2008) meeting that the 28-day dog study is acceptable and can be considered for setting the ARfD value.

2.4 GENOTOXICITY

In the DAR, four *in vitro* studies and one *in vivo* study have been evaluated and presented. Ethephon induced point mutations in *S. typhimurium* tester strain TA 1535 in the absence and presence of metabolic activation. In the other *S. typhimurium* tester strains TA 98, TA 100, TA 1537 and TA 1538, ethephon was negative, both with and without metabolic activation. Ethephon was negative in a gene mutation test with Chinese hamster ovary cells, an UDS test with rat hepatocytes and a chromosome aberration test with Chinese hamster ovary cells. Ethephon was also negative in the *in vivo* UDS test in rats. Despite some drawbacks, the in vitro studies gave negative results, with the exception of one positive strain the Ames test. Considering the overall negative results of the *in vitro* studies in combination with the negative results of the recently performed *in vivo* UDS test, ethephon is considered to be non-genotoxic.

2.5 LONG TERM TOXICITY

The long term toxicity and carcinogenic potential of ethephon were assessed in one long term study in rats and one in mice.

In a 24-months combined chronic toxicity/carcinogenicity study in rats, the main effect of ethephon administration was a dose-dependent inhibition of plasma and erythrocyte ChE activities, noted at all dose levels. At the lowest dose of 13-16 mg/kg bw/d, the inhibition was considered not biologically significant (<20%). Complete recovery of plasma and erythrocyte CHE activity to control values was not observed in animals at 446 mg/kg bw/day and higher, and maintained under control conditions for 4 weeks following 52-week exposure. The observed inhibition of brain ChE activity (< 9%) was not considered biologically significant.

In the 18 months carcinogenicity study in mice, ethephon was determined to be a potent inhibitor of plasma and erythrocyte ChE activity with dose-related inhibition. At the lowest dose of 14-17 mg/kg bw/d, the inhibition was considered not biologically significant (<20%). Brain ChE activity was inhibited by 18% in females at the highest dose level after 52 weeks. Two tumour types in males (hepatocellular adenoma and lung adenoma) and two types in females (thymic region lymphosarcoma and lung adenoma) were observed in frequencies above 5%, but only the increased incidence of lung adenomas in males at 1477 mg/kg bw/day reached the level of statistical significance. Since lung

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adenomas commonly occur in this strain of mouse and no dose-response was observed, these findings were not considered to be related to treatment.
Overall, ethephon was considered not carcinogenic.

The relevant long term NOAEL is 13 mg/kg bw/d in the rat, based on inhibition of erythrocyte ChE activity.

2.6 REPRODUCTIVE TOXICITY

An oral two-generation study in the rat in order to determine the reproductive effects of ethephon is presented and evaluated in the DAR. Decreased pup weight and survival was observed at parentally toxic doses. No effects on mating performance or fertility were noted. Initially the rapporteur Member State suggested a developmental and parental NOAEL of 23 mg/kg bw/d. However, as indicated by one MS, these NOAELs were based on very slight effects on body weight and food consumption, and after re-evaluation were considered not adverse. Therefore, the relevant NOAEL for reproduction toxicity was set at >2444 mg/kg bw/d. and the relevant NOAELs for parental and developmental toxicity were set at 231 mg/kg bw/day. The NOAEL for parental toxicity is tentative, because no ChE measurements in plasma, erythrocytes and brain were performed. No fertility effects were observed.
In order to examine teratogenic or developmental effects of ethephon one study in rat and one in rabbit were presented in the DAR.
In the teratogenicity study in rats, no treatment-related effects on dams nor on foetuses were observed. In the teratogenicity study in rabbits, increased pre- and post-implantation loss, reduced number of live foetuses, and reduced foetal weight were observed at a dose level which caused severe maternal effects (17 out of 22 test-substance related deaths). There were no test material-related foetal external, soft tissue, or skeletal variations or malformations. The relevant maternal and developmental NOAEL is 125 mg/kg bw/d in the rabbit. The NOAEL for maternal toxicity is tentative, because no ChE measurements in plasma, erythrocytes and brain were performed.

2.7 NEUROTOXICITY

In an acute neurotoxicity study in rats, no NOAEL was established, due to the dose-related increase in the incidence of miosis at all dose levels (NOAEL <500 mg/kg bw). In a 90-day neurotoxicity study in rats, the NOAEL was set at 75 mg/kg bw/day, based on the biologically significant inhibition of erythrocyte acetylcholinesterase at 150 mg/kg bw/day and above. The experts concluded that ethephon showed no potential to induce delayed neuropathy (NOAEL >1428 mg/kg bw/d). The rapporteur Member State proposed to change “neuropathy“ into “neurotoxicity“.

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2.8 FURTHER STUDIES

Toxicity studies on metabolites

An acute oral toxicity study and three in vitro genotoxicity studies were performed with the metabolite 2-hydroxyethylphosphonic acid (HEPA). The acute oral LD_{50} of HEPA was found to be >2000 mg/kg bw. HEPA was non-genotoxic in S. typhimurium tester strains TA 98 TA 100 TA 1535 TA 1537 TA 102, in a TK assay in mouse lymphoma cells and in a chromosome aberration test with Chinese hamster ovary cells. In an oral 28-day toxicity study in rats, HEPA caused, among others, mortality at 1000 mg/kg bw/d, hence the NOAEL was set at 350 mg/kg bw/d.

In the expert meeting it was concluded that HEPA is a toxicological relevant metabolite. Studies are difficult to compare, since in the 28d rat HEPA study, ChE activity was not measured. However, in the 28d study with HEPA, mortality was observed at levels at or below the LOAEL for effects other than ChE inhibition in the 28d study with ethephon. Moreover, although HEPA is found in the rat (liver and kidney), it was found at very low levels, and below the ethephon levels in those organs. Based on these studies HEPA was considered by the experts more toxic than ethephon by a factor of two. The rapporteur Member State does not agree to this position and considers HEPA as toxic as ethephon. Recently, in a communication to the rapporteur Member State, the applicant considered HEPA less toxic than ethephon based on other studies presented in the DAR; the rapporteur Member State reiterated its view of both HEPA and ethephon showing equal toxicity. Nevertheless, since this information has not been peer reviewed it cannot be considered in this stage.

Human volunteer studies

Four human volunteer studies with ethephon were submitted; one dose-range finding study and three subacute oral studies.

The individual studies with human volunteers were considered of limited value for the overall evaluation of ethephon. No additional information could be provided by the notifier on the methodology of ChE measurements. However, considering the results of all human studies with ethephon together, the data might be used for the overall evaluation of ethephon. Based on a comparison of the NOAELs and LOAEL in the human volunteer studies, and taken into consideration the NOAELs in the studies with experimental animals and the recent JMPR evaluation on ethephon, an overall NOAEL of 0.5 mg/kg bw/day was established for short term studies with human volunteers.

Mechanistic data

A statement was provided by the notifier in which the toxicological and regulatory significance of cholinesterase inhibition as associated with ethephon was described. See DAR for the statements and the response of the rapporteur Member State.

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2.9 MEDICAL DATA

No relevant data.

2.10 ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) and ACUTE REFERENCE DOSE (ARfD)

The experts discussed whether the derivation of the ADI, ARfD and AOEL had to be based on the animal data, or on the human data.

ADI and AOEL

In the meeting it was agreed that the **ADI and AOEL were to be set at 0.03 mg/kg bw/d** , based on the NOAEL of 27 mg/kg bw/d in the 1-year dog study and supported by human data. A safety factor of 1000 was used including an extra factor of 10 since ChE activity was not measured in the dog study.

ARfD

The conclusions from the EPCO 28 meeting (2005) were as follows:

ChE inhibition is considered a relevant end-point for deriving an ARfD for ethephon. The lowest ARfD will be calculated when the 1-year study in dogs (NOAEL: 27 mg/kg bw/day) is used as a starting point. Usually a 1-year dog study is not considered suitable for deriving an ARfD. However, in the Expert Meeting it was decided that, taken together all data, this was the most appropriate study in the most sensitive species relevant to humans.

In the meeting it was agreed that the **ARfD was to be set at 0.03 mg/kg bw/d**, based on the 1-year dog study, supported by human data. A safety factor of 1000 was used, including an extra factor of 10 based on the fact that ChE activity was not measured in the 1-year dog study, and the 14-day dose range finding study in dogs indicated effects on brain ChE in the absence of other clinical effects.

The conclusions from the PRAPeR 19 meeting (2007) were as follows:

In the addendum 1 on ARfD submitted in October 2006, the 28-day study in dogs was presented. The rapporteur Member State proposed an ARfD of 0.1 mg/kg bw based on the acute neurotoxicity study in rat with a LOAEL of 500 mg/kg bw. An additional safety factor of 10 was proposed due to the use of a LOAEL. As the resulting ARfD would be equal to the NOAEL in humans (0.5 mg/kg bw), another factor of 5 was applied, resulting in an overall safety factor of 5000. The experts at the PRAPeR 19 meeting considered that the margin of safety between the effects seen in humans at 1.5 mg/kg bw and the proposed ARfD was low. The high safety factor proposed reflected the limited reliability of the rat study, and the dog should still be considered the most sensitive species. Therefore the meeting confirmed the previous value of 0.03 mg/kg bw/d for the ARfD set by the experts at the EPCO 28 meeting in 2005.

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The conclusions from the PRAPeR 54 meeting (2008) were as follows:
In March 2008 the issue was discussed in the SCFCAH[6] to propose a re-evaluation of the ARfD on the basis of the complete available data set. In order to make the process transparent and to avoid misunderstanding and unreliable scientific decisions, re-discussion was agreed in 2008. The rapporteur Member State provided the addendum 2 on ethephon's ARfD in June 2008. In this document, a new approach was proposed to consider the NOAEL from 28-day dog study of 6 mg/kg bw/d and apply a standard safety factor of 100 resulting in a value of 0.06 mg/kg bw. Considering that a minimum margin of safety of 10 fold should be applied to the overall NOAEL obtained from human studies (0.5 mg/kg bw), the ARfD value should be decreased to 0.05 mg/kg bw. The PRAPeR 54 meeting agreed with this approach and **the ARfD value for ethephon was set at 0.05 mg/kg bw.** This value is in line with the JMPR value set in 2002 of 0.05 mg/kg bw based on the NOAEL from human studies and a safety factor of 10.

2.11 DERMAL ABSORPTION

In the addendum to the DAR, the dermal absorption for (dilutions of) Cerone SL was based on *in vitro* and *in vivo* studies: 3% dermal absorption can be used for the concentrate (4.8 mg/cm^2 = 1:1 dilution and 0.48 mg/cm^2 = 1:10 dilution) and 1.5% dermal absorption for the spray dilution (0.048 mg/cm^2 = 1:100 dilution).

2.12 EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The representative plant protection product Cerone SL contains 480 ethephon/L. According to the applicant the representative use is as a growth regulator in cereals (wheat and barley). CERONE SL is applied outdoors by a field crop sprayer. Downward spraying by mechanical techniques will be considered. In the addendum to the DAR new exposure calculations and risk assessments are presented.

The dermal absorption value of 3% for the concentrate and 1.5% for the dilution, and the AOEL of 0.03 mg/kg bw/day are used in the calculations.

Operator exposure

The estimated operator exposure is below the AOEL of 0.03 mg/kg bw/day for mechanical downward spraying in cereals without PPE (DE-GM) and with PPE (UK-75th), see table below.

Estimated operator exposure presented as % of AOEL (0.03 mg/kg bw/day), according to calculations with the German and UK POEM model. The default for body weight of operator is 70 kg in the German model and 60 kg in the UK-POEM model.

[6] Standing Committee on the Food Chain and Animal Health - Phytopharmaceuticals

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Model	No PPE	With PPE*:
German	48%	2%
UK POEM	172%	25%

*PPE (personal protective equipment)

Worker exposure

Based on the use of Cerone SL in cereals, no re-entry activities with intensive crop contact are anticipated after application. Therefore a worker re-entry risk assessment is not considered necessary.

Bystander exposure

The estimated bystander exposure is below the AOEL of 0.03 mg/kg bw/day for mechanical downward spraying in cereals without PPE according to EUROPOEM II, see table below.

Estimated operator exposure presented as % of AOEL (0.03 mg/kg bw/day), according to calculations with the EUROPOEM II model. The default for body weight of operator is 70 kg in the EUROPOEM II model.

Model	No PPE
EUROPOEM II	5%

3. Residues

Ethephon was discussed at EPCO experts' meeting for residues (EPCO 29) in June and July 2005.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

Plant metabolism studies with radio labelled ethephon on wheat, tomatoes and pineapple were submitted. Additional information was available on the fate of ethephon after application to squash, cucumber, apple and cherry trees. The studies indicated that metabolism of ethephon in plants mainly proceeds via conversion to 2-hydroxyethyl phosphonic acid (HEPA) and via decomposition to ethylene, which is released in the atmosphere, and phosphate which is taken up in the natural phosphate cycle of the plant. As the representative use is on cereals, the plant metabolism study on wheat is the most relevant study for evaluation related to the Peer Review of ethephon for Annex I inclusion. This study show that in the edible part (grain) of cereals treated at normal field rate, the metabolite HEPA and ethephon are present at similar levels. It is noted that the relative amount of HEPA increases in time, which may be important for the use as fruit ripening agent in e.g. tomato, cherry and pine apple since relatively high levels of HEPA might be present at harvest and possibly increase even after harvest. However, data on other crops than cereals gave no consistent results.

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Since not enough information is present about this important issue, the proposed residue definition accounts for cereals only and was proposed as ethephon and HEPA for risk assessment.
The experts' meeting for residues concluded that the structure of ethephon and HEPA were very similar and therefore, in absence of further information on the toxicology, these components might be of similar toxicity. The meeting also discussed the profile of ethephon and HEPA in metabolism study and residue trials with cereals. Finally the experts concluded that for monitoring and MRL setting purposes a residue definition in cereals as ethephon only would be sufficient, and that a conversion factor of two should be applied for cereals to account for the two different residue definitions proposed. However, in the experts' meeting for toxicology it was concluded later that HEPA is not only a toxicological relevant metabolite, but also more toxic than ethephon by a factor of two, which is not agreed by rapporteur Member State. (refer to 2.8) Further consideration on whether or not HEPA is more toxic than ethephon and needs to be also included in the residue definition for monitoring might be necessary.

Supervised residue trials on wheat and barley in the field, conforming to the critical GAP, have been evaluated. The submitted trials cover use in Northern and Southern regions of Europe. All trials were reported in sufficient detail and were supported by acceptable analytical information. Ethephon and HEPA were the residues determined in all trials relevant for the evaluation of the representative uses.
Based on the trials, low levels in wheat and barley of both, ethephon and the metabolite HEPA, are anticipated. The trials are sufficient to propose MRLs for wheat and barley grain and to assess consumer exposure to ethephon and HEPA.

Ethephon levels appeared to be stable during pasteurisation, whereas during baking, boiling, brewing and sterilisation ethephon is mainly degraded to ethylene. Processing of cereals results in concentration of ethephon in bran, shorts, germ and wheat red dog.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

A rotational crop study was submitted with ethephon on radishes, collards and wheat. ^{14}C-ethephon steadily declined in soil. Radioactivity in mature plant samples paralleled or decreased at an even faster rate compared to the soil levels. In plant extracts, no radioactive peaks greater than 0.01 mg/kg were detected. Very low levels of ethephon and 2-hydroxyethyl phosphonic acid were detected in certain samples of the crops examined (radishes, collards and wheat). The radioactivity found in plant matrices was attributable to incorporation into all categories of biomolecules. Following application of ethephon according to GAP on cereals no residues are expected in follow up crops.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

Since animal intakes (due to straw residues) were calculated as significant for cattle, a metabolism study with ruminants was required.

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Lactating goats, exposed to ethephon showed significant amounts of the ethephon being degraded to ethylene and respired CO_2. The absence of ethephon and metabolite 2-hydroxyethyl phosphonic acid (HEPA) in various matrices as well as considerably high amounts of ^{14}C in fat, protein, ethylene and CO_2 demonstrated the metabolic degradation of ethephon through an acetate-like intermediate in the tricarboxylic acid cycle. Taking into account the overdosing in this study of at least 12N and the supporting evidence that radioactivity is found to a high extent in protein, fat, ethylene and CO_2, it is concluded in the EPCO 29 meeting that ethephon is hydrolysed to lose it's chlorine and phosphate groups and that the carbon units are taken up in the tricarboxylic acid cycle, to yield natural products like fat, protein, carbohydrate and CO_2. Ethephon and HEPA are the only likely toxicological relevant compounds. Highest residue levels were found in liver (1.0 mg/kg) of which 0.15% was considered ethephon and/or HEPA (max. 0.0015 mg/kg at 12N).

Based on the representative uses evaluated and the livestock data submitted no significant residues of ethephon and HEPA are expected to occur in edible animal matrices and therefore MRLs and a respective definition to monitor those MRLs are currently not necessary for animal products.

Even though not triggered, a 28 days livestock feeding study with ethephon in cows was submitted and evaluated. This study, approximating to *ca* 50N estimated residue intake by the animals, showed that ethephon residues (HEPA was not analysed for) accounted for <0.01, <0.01, 0.64 and 0.095 mg/kg in milk, muscle, kidney and liver, respectively. Highest residues were found in kidney and the theoretically estimated residue level might rise up to 0.01 mg/kg. Thus, when new uses will be added in future, the need for MRLs has to be reconsidered. In case the residue definition for monitoring purposes in animal products should be ethephon, information about the ratio between ethephon and HEPA in animal products will be necessary to derive a factor for conversion to the residue definition for risk assessment, which is proposed as sum of ethephon and 2-hydroxyethyl phosphonic acid (HEPA).

Even though not triggered by the representative uses currently under evaluation, a metabolism study with poultry was submitted as additional information an evaluated in the DAR.

Since metabolism in ruminants and rats is similar, studies performed with pigs are not required.

3.3. Consumer risk assessment

The chronic dietary risk assessment for consumers is based on the Theoretical Maximum Daily Intake (TMDI) calculation with consumption data from the WHO/GEMS Food European diet and the Dutch model (RIKILT-DLO, the Netherlands). The acute dietary risk assessment for consumers is based on the National Estimated Short Term Intake (NESTI) calculation with consumption data from the Dutch model (RIKILT-DLO, the Netherlands). In the calculations the rapporteur Member State used the proposed ethephon MRL for wheat and barley and the proposed conversion factor of two for cereals to account for the level of HEPA residues not covered by the MRL.

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The contribution to the ADI of 0.03 mg/kg bw is less than 4 % , and acute exposure to cereals does not exceed 2% of the ARfD of 0.05 mg/kg bw for the considered consumer subgroups of adults, general population and 1-6 years old children, respectively.
Taking into account for HEPA residues corrected by a factor of two to account for its higher toxicity, the increase of the estimated consumer intake of ethephon toxicological equivalents is negligible due to the very low HEPA levels found in cereals and the overestimated exposure to ethephon residues by using the MRL in the respective intake assessments.

3.4. Proposed MRLs

Cereals	Barley, wheat	0.1 mg/kg

EU MRLs have been established for a number of commodities. They are currently being revised. Furthermore, a range of Codex MRLs has been established and will be taken into account during the European harmonisation of MRLs.

4. Environmental fate and behaviour

Ethephon was discussed at the EPCO experts' meeting (EPCO 26) in June 2005. In the environmental fate and behaviour section of the DAR, volume 1 reflects only the representative use supported by available data (wheat and barley). However, volume 3 contains all the initially notified uses information to facilitate for use on Member State level (cereals, cherries, tomato, cotton and pepper).

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

Degradation of ethephon in soil under aerobic dark conditions (20 ºC and 45% MWHC) was investigated in 4 soils. The soils covered a range of pH (5.9-7.6), clay contents (9.4-32.8 %) and organic matter content (3.4-8.3 %). Radio-labelled ethephon (both C-atoms) was applied at a field application rate of 2.24 kg/ha. Additionally one of the soils was tested at 10 °C. A second study[7] was performed with another soil (clay loam, pH 8.2, clay 32.2%, OM 4.8) to improve the overall radioactivity, which was not maintained throughout the experimental period of 180 days in the earlier study.
In aerobic conditions ethephon is degraded to form ethylene gas (up to 62% AR after 150 days), 2-hydroxyethanephosphonic acid (2-HEPA) (< 10% AR) and unextractable soil residues. Very low mineralisation (< 1% AR after 180 d) was observed in the first study. In the second study the evolution of carbon dioxide increased from 3.2% AR at day 7 up to 22.3% AR at the final sampling time (44 days). After 100-102 days, amount of non-extractable residues was in the range 11.0-53.4%

[7] The study (Fitzmaurice M.J., 2003. [^{14}C]-Ethephon: Route and Rate of Degradation under Aerobic Conditions in One Soil at 20 ºC, report C033199) was summarized in an addendum dated May 2005.

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AR. The observed decreasing of total recovery in this study (below 70% AR after approximately 102 days) was mainly due to inefficient trapping of ^{14}C-ethylene. In the second study, where a different approach to the trapping of volatile degradation products was adopted, the amount of non-extractable radioactivity increased from 8.9% initially to 27.0% AR at the final sampling time (44 d), having reached a maximum of 34.0% at 21 days.

Degradation under dark anaerobic conditions at 20 ºC was investigated in a clay loam soil over a period of 30 days. Results indicated that degradation occurred under anaerobic conditions and no major metabolites (> 10% AR) were present in the soil.

Degradation of ethephon in soil is slightly enhanced by irradiation. First order DT_{50} values recalculated by the rapporteur Member State were 16.5 days for the irradiated system and 20.7 days for the non-irradiated system. The degradation pathway did not differ between the two treatment systems. The main metabolite formed in the soil was 2-hydroxyethanephosphonic acid (2-HEPA), reaching a maximum of 10.6% AR at 10 days in the irradiated experiment and 5.7% AR at 30 days in the non-irradiated experiment.

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Degradation rate of ethephon was investigated in the same degradation studies used to establish the soil metabolism. First order DT_{50} and DT_{90} values were recalculated by the rapporteur Member State excluding data below 10% AR. The DT_{50} values at 20 ºC were 2.7 d (at pH 7.6), 22.2 d (at pH 6.9), 14.2 d (at pH 6.8) and 37.6 d (at pH 5.9). The DT_{50} value at 10 ºC was higher (51.4 d) than the DT_{50} for the same soil at 20 ºC. In the fifth soil (pH 8.2), the rate of degradation was calculated using ModelManager First Order Multi Compartment model, resulting in a DT_{50} of 6.5 days.

Under anaerobic conditions (pH 7.3), first order DT_{50} value calculated by the rapporteur Member State was 2.2 days.

A field dissipation study was carried out in the U.S.A for the representative use (spring wheat) as well as other uses (tomatoes and cotton). Different formulation (all liquid concentrates, but different in composition) were applied at each location. Following application residues of ethephon declined with time: from 0.73 mg/kg after application to 0.01-0.03 mg/kg within 60-120 days. The majority of the residues were found in the top soil (0-15 cm) except for one trial, probably due to an excessive irrigation shortly after application. Dissipation followed first order non-linear kinetics, with DT_{50} and DT_{90} values ranging from 6.8 to 20 days and from 22 to 66 days, respectively.

PECsoil values for ethephon were calculated in the original DAR for all the initially notified uses. For the representative uses (cereals) PECsoil were recalculated in an addendum (January 2006) assuming 50% and 70% crop interception values for southern and northern Europe, respectively. Time weighted average PECsoil values were based on a worst-case DT_{50} field value of 20 days. The input parameters for PECsoil calculations were confirmed by experts meeting EPCO 26. Ecotoxicological risk assessment was based only for cereals in northern Europe.

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4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Batch adsorption/desorption studies are available for ethephon and the soil metabolite 2-hydroxyethylphosphonic acid (2-HEPA) in four soils and an aquatic pond sediment. ^{14}C-ethephon can be characterized as having low mobility in silt loam soil and sandy loam pond sediment, and as being slight mobile in clay, loamy sand and sandy loam soils that were equilibrated in the dark for 24 hours at 25 ºC. Freundlich adsorption values (K_{ads}) were in the range 2.37 – 57.33, and the respective K_{oc} values were 608, 1676, 3117, 4078, and 3220 L/kg. The adsorbed substance did not undergo significant transformation during the desorption period. The metabolite 2-HEPA was classified in the low mobility to immobile categories, with K_{foc} values in the range 1464 – 5656 L/kg for all soils and 12055 L/kg for the pond sediment. No pH dependence was observed for both the parent and the metabolite 2-HEPA.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

In sterile aqueous buffer solutions, ethephon hydrolyses under all pH conditions. Under neutral and alkaline conditions it degrades rapidly (non-linear regression DT_{50} values recalculated by the rapporteur Member State: 1.7 day and 0.93 day for pH 7 and pH 9, respectively). However, ethephon was stable towards hydrolytic degradation in a sterile pH 5 buffered solution, and has a calculated half-life as given by the rapporteur Member State of approximately 66 days (extrapolated value as 50% hydrolysis was not reached). Ethylene gas was the only labelled degradate detected under all three pH conditions, together with phosphoric acid.

Aqueous photolysis is not expected to contribute to the degradation of ethephon in the environment. Ethephon was stable towards photodegradation in a sterile pH 5 aqueous buffered solution exposed to continuous artificial sunlight for 15 days at 25 ºC. Two degradates, ethylene gas and phosphoric acid, were identified in both the irradiated samples and in the dark controls and are attributed to hydrolysis. There were no distinctive photolytic products formed. For irradiated samples, an extrapolated DT_{50} value of 29.4 days was calculated based on continuous radiation.

A study on ready biodegradability was summarized in an addendum (May 2005). Results showed that ethephon was not ready biodegradable.

Water/sediment studies were conducted in two water/sediment systems. Ethephon disappeared rapidly in both systems, with ethylene as the major (volatile) radioactive metabolite (> 95% after 30 days). First order DT_{50} and DT_{90} values were calculated by the rapporteur Member State excluding values < 10% AR. Ethephon degraded in the whole system with DT_{50} values (2.6 and 2.2 days) similar to those found in the hydrolysis experiment, indicating that the route of degradation was biotic. Due to the limited quantities of ethephon that were present in the sediment phase (max. 6% AR after 4 days), no kinetic analysis was possible for this phase.

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PECsw and PECsed (the latter provided in an addendum dated May 2005) estimations were performed based on drift as the entry route to surface water at a distance of 1, 5 and 10 meters. In the original DAR calculations for all the initially notified uses (orchards, cotton and fruit vegetables) are available.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Predicted environmental concentrations in groundwater (PECgw) were calculated by the applicant using FOCUS PRZM 2.3.1 model for nine groundwater scenarios. The rapporteur Member State disregarded the study and provided FOCUS-PEARL modelling of the proposed applications with different input parameters (DT_{50}, Koc and application rate). A worse DT_{50} value of 19.2 days, in place of the appropriate mean laboratory value of 16.5 days, was used in the modelling. Evidence from both the modelling studies indicated that for the representative uses assessed, ethephon is not expected to be present in groundwater at concentrations above the drinking water limit of 0.1 µg/L. The assessment of the EU representative uses may not be considered finalised with respect to the potential for groundwater contamination, since no PECgw calculations were performed with a 50% interception value by cereals for southern Europe. However, based on the results for tomatoes with 50% crop interception summarised in Vol. 3 of the DAR, EFSA is the opinion that it is very unlikely that the trigger of 0.1 µg/L would be exceeded.

4.3. FATE AND BEHAVIOUR IN AIR

Photochemical oxidative degradation of ethephon is 10.16 days (DT_{50}). Ethephon has a low volatility (Henry's Law constant is $< 1.45 \times 10^{-7}$ Pa m^3mol^{-1}, suggesting that the concentrations of ethephon in air are likely to be negligible. Ethylene is volatile (estimated Henry's Law constant is 1.08 Pa m^3mol^{-1}), with a half-life time (Atkinson) calculated with EPI-WIN v. 3.10 of 1.26 days (assuming 12 hours light per day).

5. Ecotoxicology

Ethephon was discussed at the EPCO experts' meeting for ecotoxicology (EPCO 27) in June 2005 in York (UK).

At the moment it is not possible for EFSA to confirm the assessment of the rapporteur Member State that the two technical materials can be regarded as equivalent from an ecotoxicological point of view as the available evaluation is limited (refer to chapter 1). The EFSA proposes to discuss in a future Experts' meeting the presentation of such an evaluation.

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5.1. RISK TO TERRESTRIAL VERTEBRATES

The risk to birds and mammals is calculated according to the Guidance Document on Birds and Mammals (SANCO/4145/2000). The representative uses are in wheat and barley starting from BBCH 37-39. This growth stage is at the end of stem elongation with the flag leaf just visible. This is considered to be what is called a 'late stage' in the guidance document SANCO/4145/2000 at which it is considered unlikely that herbivorous birds and mammals will feed on the treated crop. Therefore the risk is only calculated for an insectivorous bird and mammal.

The risk to birds and mammals was revised in the addendum of May 2005 according to the latest version of the guidance document SANCO/4145/2000.

The acute, short and long term risk to insectivorous birds from exposure to ethephon in wheat and barley is considered to be low as the TER values (29.4, >31 and 11 respectively) are above the Annex VI trigger value. This was agreed by the EPCO experts' meeting.

It was noted by the rapporteur Member State that the acute endpoint for mammals, used in the risk assessment in the DAR, was not corrected for the purity of the a.s. This was corrected by the rapporteur Member State in the revised addendum of January 2006. The EFSA agrees with this revision. The outcome of the risk assessment remains unchanged: the acute and long term risk to insectivorous mammals from exposure to ethephon in wheat and barley is considered to be low as the TER values (368 and 15.2 respectively) are above the Annex VI trigger value. This was agreed by the EPCO experts' meeting.

As the logPow is below 3 the risk from secondary poisoning to birds and mammals is considered to be low.

An assessment of the risk to birds and mammals from consumption of contaminated drinking water is available in the addendum of May 2005. For birds a potential acute risk was identified in this first tier risk assessment. This was discussed at the EPCO experts' meeting. The meeting agreed that based on a weight of evidence approach (no axil water in cereals, still first tier risk assessment, late growth stage and calculation based on high water demand of laboratory birds) that although the TER is below 10 the risk to birds from this exposure route is considered to be low. The acute TER for mammals for this exposure route is 27. The EPCO experts' meeting regarded the risk to mammals from contaminated drinking water to be low.

5.2. RISK TO AQUATIC ORGANISMS

Algae and *Lemna gibba* were the most sensitive species tested on an acute time scale and fish was the most sensitive species tested on a chronic time scale. *Scenedesmus subspicatus* and *Oncorhynchus*

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mykiss were tested with the formulation EXP03725A. This formulation contains 484 g a.s./L and is considered comparable to the lead formulation Cerone.
All resulting TER-values are above the corresponding Annex VI trigger values indicating a low acute and long term risk to aquatic organisms from the representative uses of ethephon evaluated without the need for risk mitigation measures.

No studies with sediment dwelling organisms are considered necessary as the a.s. was found at concentration below 10% after 14 days in the water sediment study and the NOEC for *D. magna* exceeds 0.1 mg a.s./L.

No major or relevant metabolites in surface water, ground water or sediment were identified.

As the logPow is below 3 the risk for bioconcentration in fish is considered to be low.

5.3. RISK TO BEES

An acute contact and oral toxicity study with ethephon is available. The resulting HQ values do not breach the Annex VI trigger value indicating a low risk to bees for the representative uses of ethephon in wheat and barley.
No study with the lead formulation is available and is not considered necessary given the low toxicity to bees from the a.s. and the low toxicity from the formulation on other non-target arthropods (see point 5.4 below).

5.4. RISK TO OTHER ARTHROPOD SPECIES

Standard laboratory studies with *Aphidius rhopalosiphi*, *Typhlodromus pyri*, *Poecilus cupreus*, and *Chrysoperla carnea* with the formulation EXP03725A are available. The formulation EXP03725A is considered comparable to the lead formulation Cerone.

Effects on mortality and reproduction were below 30% for *P. cupreus*.
To address the effects seen in the laboratory on *A. rhopalosiphi, T. pyri* and *C. carnea*, an extended laboratory study with both species was submitted. The study on *A. rhopalosiphi* was performed with the formulation EXP31039C. It was agreed by the EPCO experts' meeting that this formulation was likely to be worst-case compared to the lead formulation. The other 2 extended laboratory studies were performed with EXP03725A. Effects were below 20% for both mortality and reproduction for all 3 species.
Based on the available studies the risk to non-target arthropods can be regarded as low for the representative uses in barley and wheat.

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5.5. RISK TO EARTHWORMS

A study on the acute and long term toxicity of ethephon to earthworms is available. It was not possible for the rapporteur Member State and the applicant to provide good evidence for the conversion of the application rate from kg a.s./ha to kg a.s./kg dry soil of the endpoint from the acute toxicity study. Therefore it was proposed to base the acute risk assessment on the chronic NOEC of 200 mg a.s./kg soil at which no effects were seen on mortality after 28 days and no effects were seen on reproduction after 56 days.

The risk assessment is based on a PECsoil of 0.192 mg a.s./kg soil for northern Europe. A lower interception factor is foreseen for southern Europe which leads to a higher PECsoil of 0.32 mg a.s./kg soil. The outcome of the risk assessment will not change if calculated with the PECsoil for southern Europe given that the TER values based on the PEC for northern Europe are more than one order of magnitude above the Annex VI trigger value. The resulting acute and long term TER values are above the appropriate Annex VI trigger values indicating a low risk to earthworms from the representative uses of ethephon evaluated.

No studies with the lead formulation are available. According to the Directive 91/414 no acute study with the lead formulation is necessary if the formulation contains only one active substance, which is the case for the lead formulation Cerone, and the toxicity can be reliably predicted from the study with the active substance. It is difficult to say if toxicity can be reliably predicted from the study with the active substance as the toxicity of the co-formulants is not known. The Guidance Document on Terrestrial Ecotoxicology states additionally that no study is necessary if the TER for the active substance is well above the trigger. The decision should always be based on a case-by-case analysis. The acute TER for ethephon exceeds 1042 which means that it is more than 100-fold above the trigger-value. Therefore no acute toxicity study with the formulation is considered necessary by the EFSA. No long term toxicity study is considered necessary as ethephon is intended to be applied only once a year and the DT_{90} field in the soil is below 100 days.

No major or relevant metabolites in soil were identified by the section on Fate and behaviour.

5.6. RISK TO OTHER SOIL NON-TARGET MACRO-ORGANISMS

No studies are considered necessary to address this Annex point as the DT_{90} field in the soil is below 100 days.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

The effects of the ethephon were tested on soil microbial respiration and nitrogen transformation. Effects were less than 25 % at day 28 at 2.56 mg a.s./kg d.w. soil (1920 g a.s/ha). This tested concentration exceeds the predicted environmental concentrations in soil and therefore the risk to soil

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non-target micro-organisms from ethephon is considered to be low for the representative uses evaluated.

No studies with the lead formulation are considered necessary as the DT_{90} field in the soil is below 100 days and effects were below 25% at 28 days for the active substance.

No major or relevant metabolites in soil were identified by the section on Fate and behaviour.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

A study on the influence of ethephon on seedling emergence, seed germination and plant vigour is available. The summary of this study and the consequent risk assessment is available in the addendum of May 2005 and corrected by the rapporteur Member State in the revised addendum of January 2006 as the results were twice corrected for the purity of the a.s. in the original addendum. This did not change the outcome of the risk assessment as this correction results in a higher TER value. The lowest ER_{50} (= 1.46 kg a.s./ha) is for lettuce for effects on plant vigour. The resulting TER of 146 indicates a low risk from ethephon to non-target terrestrial plants. This was agreed by the EPCO experts' meeting.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

The respiration rate EC_{50} for ethephon exceeds 716 mg a.s./L. Based on this study the risk to biological methods of sewage treatment is considered to be low for the representative uses of ethephon evaluated.

6. Residue definitions

Soil

Definitions for risk assessment: ethephon

Definitions for monitoring: ethephon

Water

Ground water

Definitions for exposure assessment: ethephon

Definitions for monitoring: ethephon

Surface water

Definitions for risk assessment: ethephon

Definitions for monitoring: ethephon

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Air

Definitions for risk assessment: ethephon, ethylene

Definitions for monitoring: ethephon

Food of plant origin

Definitions for risk assessment: ethephon + 2-hydroxyethyl phosphonic acid (HEPA); applicable to cereals only

Definitions for monitoring: ethephon with a conversion factor monitoring to risk assessment of 2 (definition and factor applicable to cereals only) [8]

Food of animal origin

Definitions for risk assessment: ethephon + 2-hydroxyethyl phosphonic acid

Definitions for monitoring: not necessary for representative uses

[8] proposal may need to be reconsideration in terms of a possible inclusion of 2-hydroxyethyl phosphonic acid (HEPA), refer to 3.1.1

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Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

Soil

Compound (name and/or code)	Persistence	Ecotoxicology
ethephon	Low to moderately persistent (first order $DT_{50\ lab}$ 2.7-37.6 d, 20°C 45% MWHC)	See 5.5, 5.6 and 5.7

Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological relevance
ethephon	Low to slight mobility (K_{foc}=608-4078L/kg)	FOCUS modelling: no trigger exceeded in all 9 scenarios Lysimeter: no data	Yes	Yes	See 5.2

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Surface water and sediment

Compound (name and/or code)	Ecotoxicology
ethephon	See 5.2

Air

Compound (name and/or code)	Toxicology
ethephon	Harmful by inhalation
ethylene	No data available

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LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- Clarification with respect to what happens to batches out of the specification (the content of one significant impurity was above the specification proposed by the applicant) as well as information to explain and clarify the specification for this impurity (AE 0764265) (date of submission unknown, data gap by the expert meeting, refer to chapter 1).
- A shelf-life study to demonstrate that the relevant impurities in the technical material are not increasing in the formulation upon storage. (date of submission unknown, data gap identified after the expert meeting taken the response from the rapporteur Member State in the evaluation table into account, refer to chapter 1)
- Depending on the final residue definition for monitoring purposes for food of plant origin, it could be necessary to require further data (refer to chapter 1 and 3).
- Batch analysis of the technical material including validated analytical methods (relevant for Phytorus, date of submission unknown, data gap identified in the DAR, refer to chapter 1).
- Purity of the starting material (manufacturing process of ethephon) (relevant for Phytorus, date of submission unknown, data gap identified in the DAR, refer to chapter 1).
- Recently, the applicant submitted a position paper reviewing the studies considered to assess HEPA toxicity. This document is available for evaluation. The outcome will be crucial to decide whether or not HEPA should be included in the residue definition for food monitoring. (refer to chapter 2 and 3)
- In 2005, the notifier was working on new information on the ARfD by performing a new short term oral dog study which may possibly lead to derivation of a higher ARfD. This study was meant to be evaluated after Annex I inclusion at the time of MRL harmonisation, to handle the acute intake problems of several fruits and fruiting vegetables. The new 28-day dietary study in dog aiming to investigate acetylcholinesterase inhibition was submitted and evaluated by the peer review in 2007-2008.

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses uses as plant growth regulator comprise foliar spraying to regulate the growth of cereals (winter wheat; winter and spring barley) at an application rate of up to 480 g ethephon per hectare ("spring": 360; "winter": 480). Ethephon can be used only as plant growth regulator.

The representative formulated product for the evaluation was "Cerone" ("EXP03725B" or "AE F013382 00 SL40"), a soluble concentrate (SL), registered under different trade names most of the Member States of the EU.

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Adequate methods are available to monitor all compounds given in the respective residue definition. Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.
It should be noted that due to data gaps it was not possible for the rapporteur Member State to conclude on the comparability of the technical materials from the second applicant.

Ethephon has an acute oral LD_{50} of 1564 mg/kg bw, an acute dermal LD_{50} of 983 mg/kg bw and an acute inhalation LC_{50} of 3.26 mg/L. Ethephon causes severe skin irritation. Hence ethephon should be classified as **'CORROSIVE'** with the associated risk phrases **[R20/21/22] 'Harmful by inhalation, in contact with skin and if swallowed'** and **[R34] 'Causes burns'**. The applicability of R43'May cause sensitisation by skin contact' was forwarded to ECB.
Ethephon is considered to be non-genotoxic and no oncogenic potential of the test substance in rats or mice was observed. There were no direct effects observed on reproductive performance or fertility. In the teratogenicity study in rabbits, no test material-related foetal variations or malformations were observed. No acute delayed neurotoxicity was observed in hens. The **ADI and AOEL were to be set at 0.03 mg/kg bw/d**, based on the 1-year dog study and supported by human data. A safety factor of 1000 was used including an extra factor of 10 since ChE activity was not measured in the study. Originally in 2005, the ARfD was also set at 0.03 mg/kg bw based on the same 1-year dog study and safety factor of 1000, however after the submission of a new oral 28-day dog study to investigate acetyl cholinesterase inhibition, this value was revised in 2007 and 2008, and considering both the dog and human studies, **the ARfD was set at 0.05 mg/kg bw.** The estimated exposure of the operator and bystanders was below the AOEL without PPE; no worker exposure is anticipated for cereals.

Following foliar application of ethephon to plants the major residue found at harvest in plant material was ethephon or its metabolite 2-hydroxyethyl phosphonic acid (HEPA). It was concluded that HEPA is of toxicological relevance and about twice more toxic than ethephon itself. Thus HEPA was included in the risk assessment for consumers. However, a reassessment of the potency of toxicity of HEPA might be needed. Due to limited data available on other crop groups the proposed residue definition and conversion factor is only applicable to cereals.
Fed to ruminants ethephon was intensively metabolised resulting in a low total residue. It was considered that ethephon and 2-hydroxyethyl phosphonic acid (HEPA) are the only possible metabolic intermediates. Studies in poultry are not triggered by the representative uses. No significant residue levels of ethephon and HEPA are expected when livestock is exposed to residues resulting from ethephon application to cereals according the evaluated cGAP.

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The chronic and acute dietary exposure assessment for consumers based on the representative GAP on cereals indicated that none of the considered consumer subgroups was exposed above 4 % of the proposed ADI and 2% of the ARfD, respectively.

The information and assessments available on the environmental fate and behaviour of ethephon were sufficient to complete an appropriate EU level environmental exposure assessment for the intended uses on cereals (wheat and barley). Ethephon is not persistent in the environment. The major degradates are ethylene gas and the non-volatile 2-hydroxyethylphosphonic acid (the latter formed at amount < 10% AR). However, based on the estimated half-life in the upper atmosphere of ethylene, long transport in the air compartment of this metabolite is not expected. For the representative uses assessed ethephon would not be expected to leach to groundwater above 0.1µg/L.

The risk to birds and mammals was assessed according to the Guidance Document on Risk Assessment for Birds and mammals Under Council Directive 91/414/EEC (SANCO/4145/2000). The risk to insectivorous birds and mammals in cereals can be regarded as low. The risk to birds and mammals from secondary poisoning and from consumption of contaminated drinking water is regarded to be low for the representative uses evaluated.
The risk to aquatic organisms is regarded to be low without the need for risk mitigation measures.
The risk to bees and other arthropod species can be regarded as low based on the available studies.
The risk to earthworms, other soil non-target macro-organisms and soil micro-organisms can be regarded as low.
The risk to non-target plants and biological methods for sewage treatment is considered to be low.

Particular conditions proposed to be taken into account to manage the risk(s) identified

- None.

Critical areas of concern

- At the moment no final specification for the technical material (technical concentrate) can be set (refer to chapter 1). In addition, for the moment it is not possible for EFSA, from an ecotoxicological point of view, to confirm the assessment of the rapporteur Member State that the two technical materials from Bayer CropSciene can be regarded as equivalent.

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APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

Appendix 1.1: Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Ethephon (No ISO common name is available, the name "ethephon" is approved by the American National Standards Institute, and the name "chlorethephon" is used in New Zealand.)
Function (e.g. fungicide)	Plant growth regulator

Rapporteur Member State	The Netherlands
Co-rapporteur Member State	--

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	2-chloroethylphosphonic acid
Chemical name (CA) ‡	(2-chloroethyl)phosphonic acid
CIPAC No ‡	373
CAS No ‡	16672-87-0
EEC No (EINECS or ELINCS) ‡	240-718-3
FAO Specification ‡ (including year of publication)	Ethephon technical: > 910 g/kg MEPHA: Mono 2-chloroethyl ester, 2-chloroethyl phosphonic acid: maximum 20 g/kg 1,2-Dichloroethane: maximum 0.5 g/kg (Specification 373/TC/S/F (2000)) Ethephon technical concentrate: The ethephon content shall be declared (g/kg). MEPHA: Mono 2-chloroethyl ester, 2-chloroethyl phosphonic acid : Maximum 2 % of the ethephon declared content 1,2-Dichloroethane: Maximum 0.04% of the ethephon declared content The product shall pass through a 250 µm test sieve and not more than 1 g/kg shall remain on a 150 µm test sieve. The water content shall be measured (g/kg), and

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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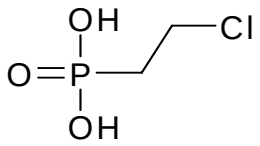
	the value obtained shall not be less than the following figure: {1000 – (measured ethephon content in g/kg)/0.91} – 15
Minimum purity of the active substance as manufactured ‡ (g/kg)	910 g/kg (technical dry material - TC) Between 692 and 735 g/kg (technical concentrate (TK), the commercial material) 692 g/kg (minimum purity TK)
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	See FAO Specification
Molecular formula ‡	$C_2H_6ClO_3P$
Molecular mass ‡	144.5
Structural formula ‡	

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	73.3 °C (98.5%)
Boiling point (state purity) ‡	Not relevant (thermal decomposition)
Temperature of decomposition	250-400 °C (under nitrogen) (98.5%)
Appearance (state purity) ‡	White crystalline powder (98.5%)
Relative density (state purity) ‡	Density: 1.65 kg/m^3 at 20 °C (98.5%)
Surface tension	68.5 mN/m at 20 °C (98.5%)
Vapour pressure (in Pa, state temperature) ‡	<1.0 x 10-3 Pa (from 18 to 80 °C) (98.5%)
Henry's law constant (Pa m^3 mol $^{-1}$) ‡	<1.45 x 10^{-7} Pa m^3 mol^{-1}solids or liquids determined or calculated from water solubility and vp (units Pa m^3 mol^{-1})
Solubility in water ‡ (g/L or mg/L at 20 °C)	At pH <0.2: >1000 g/L at pH 4: 800 g/L. Above pH 5: decomposition and no solubility could be determined

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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Solubility in organic solvents ‡ (in g/L or mg/L, state temperature)	Purity 98.5%: *n*-heptane <0.3 mg/L at 20°C *p*-xylene 82.5 mg/L at 20°C 1,2-dichloroethane 832 mg/L at 20°C methanol >600 g/L at 20°C acetone >600 g/L at 20°C ethyl acetate >600 g/L at 20°C acetonitrile >600 g/L at 20°C dimethylsulfoxide >600 g/L. at 20°C
Partition co-efficient (log P_{OW}) ‡ (state pH and temperature)	Purity 98.5%: log P_{ow} = -0.63 at pH 2, room temperature log P_{ow} = -1.89 at pH 7, room temperature log P_{ow} = -1.81 at pH 10, room temperature
Hydrolytic stability (DT_{50}) ‡ (state pH and temperature)	97.5% radio chem. pure: Half life at 25 °C: at pH 5 73.5 days at pH 7 2.4 days at pH 9 1.0 day (linear-regression)
Dissociation constant ‡	Purity 98.5%: pK_1 = 2.82 at 21 °C pK_2 = 7.21 at 21 °C
UV/VIS absorption (max.) ‡ (if absorption > 290 nm state ε at wavelength)	At 195 nm: ε = 33 At 295 nm: ε = 0,4 No absorption above 290 nm.
Photostability (DT_{50}) ‡ (aqueous, sunlight, state pH)	Ethephon (at 25 °C and pH 5): rate constant k_2 under irradiated conditions 9.39 10^{-04} h^{-1} (DT_{50} 61 days of 12 hr irradiation/day). rate constant k_1 under non-irradiated conditions 5.22 10^{-04} h^{-1} (DT_{50} 111 days of 12 hr darkness/day). Net rate constant k_3 (DT_{50}) due to irradiation alone: $k_3 = k_2 - k_1$ = 4.17E-04 h^{-1} (Net half-life 139 days of 12 hr irradiation/day). (Linear-regression) Only degradation product is ethylene, max. 15.3% and 23.1% in non-irradiated and irradiated samples,

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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	respectively.
Quantum yield of direct phototransformation in water at Σ > 290 nm ‡	No data required since photolysis is insignificant (see above)
Flammability ‡	Purity 71.4% / 70.2%: no flash point up to 111 °C (boiling temp.) self ignition temperature: 490 °C
Explosive properties ‡	Purity 70.2%: not explosive

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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List of representative uses evaluated*

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 a.s. (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		
Cereals: wheat (winter)	EU South	Cerone	F	Growth regulation	SL	480 g/L	Foliar spraying	BBCH 37-39 (maxi)	1		0.24	200	0.48	Cf. growth stage	PHI: treatment period is determined by growth stage
Cereals: wheat (winter)	EU North	Cerone	F	Growth regulation	SL	480 g/L	Foliar spraying	M-N Baggiolini scale (BBCH 41-51)	1		0.24	200	0.48	Cf. growth stage	PHI: treatment period is determined by growth stage
Cereals: barley (winter and spring)	EU South	Cerone	F	Growth regulation	SL	480 g/L	Foliar spraying	BBCH 37-39 (maxi)	1		S: 0.18 W: 0.24	200	S: 0.36 W: 0.48	Cf. growth stage	PHI: treatment period is determined by growth stage

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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 a.s. (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		
Cereals: barley (winter and spring)	EU North	Cerone	F	Growth regulation	SL	480 g/L	Foliar spraying	M-N Baggiolini scale (BBCH 41-51)	1		S: 0.18 W: 0.24	200	S: 0.36 W: 0.48	Cf. growth stage	PHI: treatment period is determined by growth stage

S: spring; W: Winter

Remarks:				
	*	Uses for which risk assessment could not been concluded due to lack of essential data are marked grey	(h)	Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
	(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)	(i)	g/kg or g/L
	(b)	Outdoor or field use (F), glasshouse application (G) or indoor application (I)	(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
	(c)	*e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds		
	(d)	*e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)	(k)	The minimum and maximum number of application possible under practical conditions of use must be provided
	(e)	GCPF Codes - GIFAP Technical Monograph No 2, 1989		
	(f)	Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench	(l)	PHI - minimum pre-harvest interval
	(g)	All abbreviations used must be explained	(m)	Remarks may include: Extent of use/economic importance/restrictions

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Appendix 1.2: Methods of Analysis

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

Technical as (principle of method)	Titration (CIPAC method 373)
Impurities in technical as (principle of method)	GC-FID; CG-ECD; Karl Fisher; Chloride titration, ion-chromatography-conductivity
Plant protection product (principle of method)	Titration (CIPAC method 373)

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	RP-LC-ESI-MS/MS Extraction with methanol/water/formic acid. Methanol/water/formic acid gradient elution on a silica-based C18 column. LOQ = 0.05 mg/kg (wheat, orange, olive, tomato)
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not required, no MRLs proposed
Soil (principle of method and LOQ)	HPLC-MS/MS Extraction with weak phosphorous acid solution. Mobile phases: water/formic acid and acetonitrile. Column: Aqua 3µ C18 125A. LOQ = 5 µg/kg
Water (principle of method and LOQ)	Empore disk extraction, followed by dissolution with a mixture of methanol and hydrochloric acid. Evaporation to aqueous residue and solvent transfer into acetonitrile and silylation of extract with MTBSTFA. Quantification by GC-MS. LOQ (mineral, tap and surface water) = 0.1 µg/L
Air (principle of method and LOQ)	Air is trapped in cartridges with silica gel, which is desorbed with a concentrated alkaline solution, liberating ethylene. Ethylene is transferred to the headspace by sonication and quantified by GC-FID. LOQ = 2 µg/m^3 (> 50 L air sample) or Air is trapped in adsorption tubes with XAD which is extracted with a mixture of methanol and formic acid Quantification by LC-MS/MS. LOQ = 1.4 µg/m^3
Body fluids and tissues (principle of method and LOQ)	No methods required, not a (very) toxic compound

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Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	Not classified

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Appendix 1.3: Impact on Human and Animal Health

Many of the toxicity studies have been conducted with Ethephon Base 250 (a liquid concentrate of c.70% ethephon in water) but all dose levels quoted here refer to ethephon.

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

Rate and extent of absorption ‡	78-84% based on radiolabel recovered in urine, tissues, cage wash, expired air/volatiles and residual carcass within 120 h.
Distribution ‡	Widely; highest residues in liver, blood and kidney at 50 mg/kg bodyweight.
Potential for accumulation ‡	No potential for accumulation
Rate and extent of excretion ‡	Extensively excreted - urinary: 50-60% in 120 h; faecal 4.0-6.5% in 120 h; and exhaled 20%
Metabolism in animals ‡	Extensively metabolised to disodium salt of ethephon, and HEPA was found in the liver
Toxicologically significant compounds ‡ (animals, plants and environment)	Ethephon and HEPA (toxicologically relevant)

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	1564 mg/kg bw;	**R22**
Rat LD_{50} dermal ‡	983 mg/kg bw;	**R21**
Rat LC_{50} inhalation ‡	3.26 mg/L air/4h (whole body);	**R20**
Skin irritation ‡	Causes burns;	**R34**
Eye irritation ‡	No data available, not considered necessary due to pH and effects (R34) of substance	
Skin sensitization ‡ (test method used and result)	Evidence of skin sensitization – inconclusive due to corrosive properties (LLNA and Maximisation test);	**R43?**

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Inhibition of cholinesterase (ChE) activity in erythrocytes
Lowest relevant oral NOAEL / NOEL ‡	28-day mouse: 22 mg/kg bw/day 1-year dog: (27 mg/kg bw/day) based on decreased body weight and spleen and thyroid weight (ChE activity in plasma, erythrocytes and

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	brain was not investigated in dogs) 28-day dog (AChE inhibition): 6 mg/kg bw/day
Lowest relevant dermal NOAEL / NOEL ‡	No good study available (not required)
Lowest relevant inhalation NOAEL / NOEL ‡	No data – not required

Genotoxicity ‡ (Annex IIA, point 5.4)

……	No genotoxic potential

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

Target/critical effect ‡	Inhibition of ChE activity in erythrocytes
Lowest relevant NOAEL / NOEL ‡	2 years rat: 13 mg/kg bw/day
Carcinogenicity ‡	No carcinogenic potential

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	Decreased pup weight (F_1 and F_2), decreased survival of F_{1B} and F_{2B} pups, at parental toxic doses (decreased body weight (gain) and food consumption).
Lowest relevant reproductive NOAEL / NOEL ‡	Parental and offspring: 231 mg/kg bw/day Reproductive: >2444 mg/kg bw/day
Developmental target / critical effect ‡	Increased pre-and post-implantation loss, reduced number of live foetuses, reduced foetal weight at maternally toxic doses (19 out of 22 deaths).
Lowest relevant developmental NOAEL / NOEL ‡	Parental and developmental 125 mg/kg bw/day (rabbit).

Neurotoxicity / Delayed neurotoxicity ‡ (Annex IIA, point 5.7)

Acute neurotoxicity (rat)	Reduced motor activity and myosis (NOAEL < 500 mg/kg bw/day)
Acute delayed neurotoxicity (hen)	No sign of delayed neurotoxicity (NOAEL > 1428 mg/kg bw/d)
Semichronic oral neurotoxicity (rat)	inhibition of ChE activity (NOAEL 75 mg/kg bw/day)

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Other toxicological studies ‡ (Annex IIA, point 5.8)

Studies with a plant metabolite (2-hydroxyethylphosphonic acid, HEPA)	- LD_{50}, oral rat: > 2000 mg/kg bw - 28d oral toxicity rat: mortality, clinical signs, decreased body weight (NOAEL 350 mg/kg bw/d) ChE activity in plasma, erythrocytes and brain was not investigated - no genotoxic potential
Human volunteer studies	Three subacute studies (capsule) were submitted. Individual studies were of limited quality. An overall NOAEL of 0.5 mg/kg bw/day was established based on clinical observations (urination, diarrhoea, bowel movements) at 1.5 mg/kg bw/day.

Medical data ‡ (Annex IIA, point 5.9)

……..	No relevant data

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.03 mg/kg bw/day	1-y oral dog, supported by human data	1000*
AOEL ‡	0.03 mg/kg bw/day	1-y oral dog, supported by human data	1000*
ARfD ‡ (acute reference dose)	0.05 mg/kg bw	28-d oral dog (AChE inhibition study), lowered to get a 10 fold MoS to the NOAEL from human data	100

* an extra factor of 10 was considered since ChE activity was not measured in the study

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Dermal absorption (Annex IIIA, point 7.3)

……..	3% for concentrate 1.5% for spray dilution based on *in vitro* human and rat and *in vivo* rat data

Acceptable exposure scenarios (including method of calculation)

Operator	Without PPE exposure is 48% of AOEL ((DE-GM model)
Workers	For cereals exposure with intensive crop contact is not expected.
Bystanders	Estimates 5% of AOEL

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	C;	corrosive
	R20/R21/R22,	Harmful by inhalation, in contact with skin and if swallowed
	R34,	Causes burns
	R43?	May cause sensitisation by skin contact
	S26,	In case of contact with eyes rinse immediately with plenty of water and seek medical advice
	S36/37/39,	Wear suitable protective clothing, gloves and eye/face protection
	S45	In case of accident or if you feel unwell, seek medical advice immediately

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Appendix 1.4: Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Cereals (wheat)
Rotational crops	Radishes, collard, wheat
Plant residue definition for monitoring	Ethephon
Plant residue definition for risk assessment	Ethephon + 2-hydroxyethyl phosphonic acid [HEPA] (cereals only)
Conversion factor (monitoring to risk assessment)	2 (cereals only)

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

Animals covered	Goat (Poultry additional)
Animal residue definition for monitoring	Not necessary for representative uses
Animal residue definition for risk assessment	Ethephon + 2-hydroxyethyl phosphonic acid [HEPA]
Conversion factor (monitoring to risk assessment)	Information will be necessary, when MRLs need to be proposed
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	No

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

……..	No significant residue levels are expected

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

……..	At –20°C, ethephon is stable in wheat grain, fresh frozen and freeze-dried tomato fruit, apple fruit, grape berries and blackberries, cottonseeds and wheat straw for 24 months and in apple juice and cottonseed oil for 12 months.

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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: yes	Poultry: no	Pig: no
Muscle	*	n/a	n/a
Liver	*	n/a	n/a
Kidney	*	n/a	n/a
Fat	*	n/a	n/a
Milk	*	n/a	n/a
Eggs	*	n/a	n/a

* based on ruminant metabolism studies significant residues (<0.01 mg/kg) are not expected, MRLs should not been set
n/a not applicable

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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)	HR
Wheat and barley (grain) ethephon	N & S	21 x <0.05, 2 x 0.05, 3 x 0.06	Since the observed residue levels in barley and wheat grain performed in the northern and southern European zones are showing comparable residue levels, the results are taken together Use STMR in dietary intake calculation livestock	0.1	0.05	0.06
Wheat and barley (grain) HEPA	N &S	25x<0.05,		-	0.05	0.05
Wheat and barley (straw) ethephon	N &S	2x<0.05, 0.06, 0.075, 0.08, 0.09, 0.12, 0.13, 0.14, 2x0.15, 0.21, 2x0.22, 0.25, 0.33, 0.36, 0.38, 0.43, 0.45, 0.46, 0.51, 0.56, 0.63, 0.95, 1.1, 1.3,	Use HR in dietary intake calculation livestock	-	0.22	1.3
Wheat and barley (straw) HEPA	N &S	25x<0.05, 0.05, 0.06	Use HR in dietary intake calculation livestock	-	0.05	0.06

(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

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

ADI	0.03 mg/kg bw/day
TMDI (European Diet) (% ADI)	Based on currently proposed MRL and conversion factor: European Diet (ITMDI) 2.2% Dutch Diet (NTMDI) general population 1.7 % Dutch Diet (NTMDI) children 1 – 6 years 3.4 %
NEDI (% ADI)	Not applicable
Factors included in NEDI	Not applicable
ARfD	0.05 mg/kg bw
Acute exposure (% ARfD)	Based on currently proposed MRL and conversion factor: Dutch Diet (NESTI) $\leq$ 2 % (adult and child)

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

Crop/processed crop	Number of studies	Transfer factor	% Transference *
Wheat grain (RAC)			
Dust	1	0.6	-
Bran	1	1.4	-
Middling	1	<0.3	-
Low grade flour	1	<0.3	-
Patent flour	1	<0.3	-
Shorts	1	1.5	-
Germ	1	1.5	-
Wheat red dog	1	1.2	-

* 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)

Wheat, barley	0.1 mg/kg

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Appendix 1.5: Fate and Behaviour in the Environment

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

Mineralization after 100 days ‡	< 1% a.r. after 180 d (14C-Ethephon, 4 soils) 22.3% a.r. after 44 d (14C-Ethephon, 1 soil)
Non-extractable residues after 100 days ‡	11-53.4% a.r. after 100-102 d (14C-Ethephon, 4 soils, incubated at 20°C) 27% a.r. after 44 d (end study) (14C-Ethephon, clay loam soil, incubated at 20 ºC) 34.9% a.r. after 180d (14C-Ethephon, Clay loam soil, incubated at 10°C)
Relevant metabolites - name and/or code, % of applied ‡ (range and maximum)	**Ethylene** 0.0 – 62.1% a.r. after 1 – 180d (4 soils, from volatile traps) 24.6 % a.r. after 44 d (1 soil, from volatile traps)

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

Anaerobic degradation	DT_{50lab} (20ºC, anaerobic; Clay loam soil) 2.2 d
Mineralisation after 100 days	0.03% a.r. after 30d (14C-Ethephon, Clay loam soil)
Non-extractable residues after 100 days	2.1% a.r. after 30d (14C-Ethephon, Clay loam soil)
Relevant metabolites - name and/or code, % of applied (range and maximum)	**Ethylene** 94.1% a.r. after 30d (14C-Ethephon, Clay loam soil)
Soil photolysis	Clay loam soil: degradation of Ethephon enhanced by irradiation; no photo-products > 10% a.r.

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

Method of calculation	First-order kinetics
Laboratory studies ‡ (range or median, with n value, with r^2 value)	DT_{50lab} (20ºC, aerobic; 4 soils) 22.2d (pH 6.9); 14.2d (pH 6.8); 37.6d (pH 5.9); 2.7d (pH 7.6); r^2 0.87; 0.96; 0.91; 0.99 resp. DT_{50lab} (20ºC, aerobic; 1 soil); 6.5d (pH 8.2). r^2: 0.99 average DT50 value: 16.5 d

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	$DT_{90\ lab}$ (20ºC, aerobic; 4 soils) 160d ; 60.7d ; 173d ; 12.5d DT_{90lab} (20ºC, aerobic, 1 soil) ; 63 d average DT90 value: 93.8d
	DT_{50lab} (10ºC, aerobic; Clay loam soil) 51.4d
	Degradation in the saturated zone: not available and not required
Field studies ‡ (state location, range or median with n value)	$DT_{50\ field}$ 1st order non-linear r2 0.96-0.99 6.8-20 d. 3 sites in USA (California, tomatoes; North Carolina, cotton; Washington, cereals) $DT_{90\ field}$ 22-66 d
Soil accumulation and plateau concentration ‡	not relevant

Rate of degradation in soil - Supplemental studies

Anaerobic degradation	DT_{50lab} (20ºC, anaerobic; Clay loam soil) 2.2 d
Soil photolysis	Clay loam soil: degradation of Ethephon enhanced by irradiation. 1st order kinetics Irradiated treatment: DT_{50} 16.5 d, DT_{90} 57.8d Non-irradiated treatment: DT_{50} 20.7 d, DT_{90} 74.4 d

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Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc} ‡ K_d ‡ pH dependence ‡ (yes / no) (if yes type of dependence)	K_F, Koc and 1/n values are listed in corresponding order of soils **Ethephon** (4 soils and 1 sediment) soiltype pH 1/n Koc [L/kg] clay 5.2 0.987 3220 Loamy sand 5.2 1.007 3117 Silt loam 5.3 1.017 608 Sandy loam 4.6 0.977 4078 sediment 6.0 0.987 1676 Average Koc 2540 L/kg no pH dependence **2-hydroxyethylphosphonic acid** (2-HEPA), (4 soils and 1 sediment) Soiltype pH 1/n Koc [L/kg] Silt loam 6.0 0.891 1499 Sandy loam 6.3 0.98 2313 Loamy sand 7.1 0.899 1464 Clay 6.3 0.972 5656 Sediment 5.9 0.974 12055 average Koc 4597 L/kg no pH dependence

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

Column leaching ‡	Not available, not required
Aged residues leaching ‡	Not available, not required
Lysimeter/ field leaching studies ‡	Not available, not required

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PEC (soil) (Annex IIIA, point 9.1.3)

Parent

Method of calculation	50% crop interception for southern Europe 70% crop interception for northern Europe 5 cm soil incorporation soil density 1.5 g/cm^3 DT_{50} used: 20d **Metabolites:** no metabolites > 10% a.r. were detected in soil.
Application rate	0.48 kg a.s./ha

Initial and TWA PECs (mg/kg) of Ethephon following application in cereals (0.48 kg a.s./ha for wheat and barley).

	Field crops wheat/barley northern Europe (0.48 kg a.s./ha)		Field crops wheat/barley southern Europe (0.48 kg a.s./ha)	
day after application	actual	TWA	actual	TWA
0	0.192	-	0.320	-
1	0.185	0.189	0.309	0.315
2	0.179	0.185	0.299	0.309
4	0.167	0.179	0.279	0.299
7	0.151	0.170	0.251	0.284
21	0.093	0.136	0.155	0.227
28	0.073	0.123	0.121	0.205
56	0.028	0.085	0.046	0.141
100	0.006	0.054	0.010	0.089

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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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 5, 25°C: 26.4% hydrolysed after 30 d, extrapolated DT_{50}: 66.4 d (DT50 at 20°C: 99.1d; Non-linear regression) pH 7, 25°C: 86.6% hydrolysed after 7 d, DT50: 1.7d (DT50 at 20°C: 2.5d Non-linear regression) pH 9, 25°C: 75.4% hydrolysed after 2d, DT50 0.93d (DT_{50} at 20°C: 1.4d Non-linear regression) Major hydrolysis product: ~~E -~~ethylene gas ~~(not quantified)~~
Photolytic degradation of active substance and relevant metabolites ‡	Buffer pH 5 with acetate, 25°C, Xenon light > 290 nm. Test duration 15 days. Extrapolated DT50 under continuous illumination: 29.4d. Non-irradiated control: extrapolated DT50: 51.4 d
Readily biodegradable (yes/no)	not ready biodegradable (study available)
Degradation in water/sediment (range or median, with n value, state temperature) - DT_{50} water ‡ - DT_{90} water ‡ - DT_{50} whole system ‡ - DT_{90} whole system ‡	**Aerobic** study with 2 water/sediment systems (from Manningtree and from Ongar), 20°C: 2.6d and 2.2d 8.5d and 7.2d 3.0d and 2.7d 9.9d and 8.6d
Mineralization	**Aerobic** study with 14C-Ethephon (2 systems), 20°C: not relevant
Non-extractable residues	**Aerobic** study with 14C-Ethephon (2 systems), 20°C: max. 3.5% and 3.6% after 30d (end)
Distribution in water / sediment systems (active substance) ‡	**Aerobic** study (2 systems), 20°C: Rapid dissipation of Ethephon from water mainly due to degradation with Ethylene as the major degradation product. Max. 98.72 % a.r. at the start and < 1% a.r. after 30 days. Low amount of residues (extracted + unextracted), bound to the sediment phase (< 5% after 30 days). Maximal amount of extractable Ethephon in sediment: 6.02 % a.r. (in the Ongar system after 4 days).

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Distribution in water / sediment systems (metabolites) ‡	Metabolites > 10% a.r.: **Aerobic** study (2 systems), 20°C: Respectively 95% and 99% a.r. was recovered from the volatile traps as trapped ethylene gas.

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

Parent

Method of calculation	Static water layer 30 cm deep DT_{50} (water) = 2.4d
Application rate	Single application at 0.48 kg a.s./ha
Main routes of entry	Entry into surface water via drift, based on 90th percentile drift values taken from Rautmann et al.

PEC_{sw} (µg/L)						
day after application	field crops cereals: PECsw of Ethephon at distance (drift %):					
	1 m (2.77)		5 m (0.57)		10 m (0.29)	
	actual	TWA	actual	TWA	actual	TWA
0	4.43	4.43	0.91	0.91	0.46	0.46
1	3.32	3.85	0.68	0.79	0.35	0.40
2	2.49	3.37	0.51	0.69	0.26	0.35
4	1.40	2.63	0.29	0.54	0.15	0.28
7	0.59	1.90	0.12	0.39	0.061	0.20
14	0.078	1.08	0.016	0.22	0.008	0.11
21	0.01	0.73	0.002	0.15	0.001	0.076
28	0.001	0.55	0.0003	0.11	0.0001	0.057

PEC_{Sed} (µg/kg dw) 6% of the dose						
day after application	field crops cereals: PECsed of Ethephon at distance (drift %)					
	1 m (2.77)		5 m (0.57)		10 m (0.29)	
	PEC actual	TWA PEC	PEC actual	TWA PEC	PEC actual	TWA PEC
0	1.28	1.28	0.253	0.253	0.128	0.128

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PEC_{Sed} (µg/kg dw) 6% of the dose						
day after application	field crops cereals: PECsed of Ethephon at distance (drift %)					
	1 m (2.77)		5 m (0.57)		10 m (0.29)	
	PEC actual	TWA PEC	PEC actual	TWA PEC	PEC actual	TWA PEC
1	0.919	1.07	0.189	0.219	0.096	0.112
2	0.689	0.932	0.142	0.192	0.072	0.098
4	0.387	0.728	0.080	0.150	0.04	0.076
7	0.163	0.527	0.033	0.108	0.017	0.055
14	0.022	0.298	0.004	0.061	0.002	0.031
21	0.003	0.202	0.001	0.042	0.00	0.021
28	0.00	0.152	0.00	0.031	0.00	0.016
42	0.00	0.101	0.00	0.021	0.00	0.011

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

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	Modelling using FOCUS-PEARL, with appropriate FOCUS gw scenarios, according to FOCUS Guidance. Scenarios: cereals (Chateaudun, Hamburg, Jokoinen, Kremsmunster, Okehampton, Piacenza, Porto, Sevilla, Thiva) Average K_{om}, 1/n and $DT_{50\ ,lab}$ values were used, 1473 L/kg, 0.995 and 19.2 days[9].
Application rate	Single application, 0.48 kg a.s./ha The dose was corrected for the maximum interception by the crop (70% for winter wheat, winter and spring barley representative only for Europe-N uses~~)~~ Time of application: May 15 (winter wheat, Europe-N), May 01 (winter wheat, barley Europe-S), June 01 (summer wheat, barley Europe-N) and May 15 (summer barley for Europe-S).

[9] Mean laboratory DT_{50} value to be use in the FOCUS GW modelling: 16.5 days.

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$PEC_{(gw)}$

Maximum concentration	-
Average annual concentration (Results quoted for modelling with FOCUS gw scenarios, according to FOCUS guidance)	Predicted 80th percentile concentrations in groundwater of <0.001 µg/L for Ethephon for all crops and scenarios tested

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

Direct photolysis in air ‡	Not available, not required
Quantum yield of direct phototransformation	Not available, not required
Photochemical oxidative degradation in air ‡	DT_{50} 10.2 ~~h~~ days (Atkinson method, 12h. day)
Volatilization ‡	Henry's Law constant: < 1.45 * 10^{-7} Pa/mol.m^3 not available, not required

PEC (air)

Method of calculation	Photochemical oxidative degradation half life of Ethephon is 10.2 days (12 hour day). It has low volatility (Henry's Law constant is < 1.45 * 10^{-7} Pa/mol.m^3), suggesting that the concentrations of Ethephon in air are likely to be negligible.

$PEC_{(a)}$

Maximum concentration	No data; not calculated

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	**Soil** Ethephon **groundwater** Ethephon **surface water and sediment** Ethephon **air** Ethylene, ethephon

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

Soil (indicate location and type of study)	Not available
Surface water (indicate location and type of study)	Not available
Ground water (indicate location and type of study)	Not available
Air (indicate location and type of study)	Not available

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	Potential for R53: May cause long-term adverse effects in the aquatic environment

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Appendix 1.6: 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} = 1564mg/kg bw
Reproductive toxicity to mammals	Overall NOAEL: 22.8 mg as/kg bw/d Ecotoxicologically relevant NOEC: 22.8 mg as/kg bw/d
Acute toxicity to birds ‡	LD_{50} = 764 mg/kg bw (Bobwhite quail) LD_{50} = 1425 mg/kg bw (Mallard duck) NOEL = 450 mg a.s./kg bw (Mallard duck)
Dietary toxicity to birds ‡	8d-LC_{50} > 450mg a.s./kg bw (Bobwhite quail) 8d-NOEL > 530 mg a.s./kg bw (bobwhite quail)
Reproductive toxicity to birds ‡	6w-NOEL = 159 mg a.s./kg bw (Japanese quail)

Toxicity/exposure ratios for **birds**
Assessment in agreement with Guidance Document on Risk Assessment for Birds and Mammals Under Council Directive 91/414/EEC (Working Document Sanco/4145/2000 - September 2002).

Acute Toxicity Exposure Ratios for exposure of birds to Ethephon, due to consumption of contaminated small insects.

application	dose (kg as/ha)	Bird type	Approx. body weight (g)	Route	DFI (g/day)	LD_{50} (mg/kg bw)	ETE (mg/kg bw/d)	TERa
Cereals (late)	0.48	Insectivorous bird	10	small insects	10.4	764	26.0	29.4

Short-term Toxicity Exposure Ratios for exposure of birds to Ethephon due to consumption of contaminated small insects.

application	dose (kg as/ha)	Bird type	Approx. body weight (g)	Route	DFI (g/day)	LD_{50} (mg/kg bw/d)	ETE (mg/kg bw/d)	TERst
cereals (late)	0.48	Insectivorous bird	10	small insects	10.4	> 450	14.5	> 31

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Long-term Toxicity Exposure Ratios for exposure of birds to Ethephon due to consumption of contaminated small insects.

application	dose (kg as/ha)	Bird type	Approx. body weight (g)	Route	DFI (g/day)	NOEC (mg/kg bw/d)	ETE (mg/kg bw/d)	TERlt
cereals (late)	0.48	Insectivorous bird	10	small insects	10.4	159	14.5	11.0

Acute Toxicity Exposure Ratios for birds drinking contaminated water from puddles.

scenario		ETE	TER
acute	cereals	1.3	5.9*

* based on a weight of evidence approach (no axil water in cereals, still first tier risk assessment, late growth stage and calculation based on high water demand of laboratory birds) the risk is considered to be low

Toxicity/exposure ratios for **mammals** (Annex IIIA, points 10.3)
Assessment in agreement with Guidance Document on Risk Assessment for Birds and Mammals Under Council Directive 91/414/EEC (Working Document Sanco/4145/2000 - September 2002).

Acute Toxicity Exposure Ratios for exposure of mammals to Ethephon due to consumption of contaminated large insects.

application	dose (kg as/ha)	Mammal type	Approx. body weight (g)	Route	DFI (g/day)	LD_{50} (mg/kg bw/d)	ETE (mg/kg bw/d)	TERa
Cereals (late)	0.48	insectivorous mammal	10	large insects	6.3	1564	4.2	368

Short-term risk assessment is conducted for birds only (in agreement with the guidance in Sanco/4145/2000).

Long-term Toxicity Exposure Ratios (First Tier) for exposure of mammals to Ethephon due to consumption of contaminated large insects.

application	dose (kg as/ha)	Mammal type	Approx. body weight (g)	route	DFI (g/day)	NOAEL (mg/kg bw/d)	ETE (mg/kg bw/d)	TERlt
Cereals (late)	0.48	insectivorous mammal	10	large insects	6.3	22.8	1.5	15.2

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Acute Toxicity Exposure Ratios for mammals drinking contaminated water from puddles.

scenario		ETE	TER
acute	cereals	0.48	27.7

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Purity	Species	Endpoint	Toxicity value	Test Guideline	Reference no.
Acute fish					
98%	Carp (*Cyprinus carpio*)	96h-LC_{50}	> 100 mg a.s./L	OECD 203 EC C.1	8.2.1.2
484 g Ethephon/L (EXP03725A)	Rainbow trout (*Oncorhynchus mykiss*)	96h-LC_{50}	> 100 mg product/L	OECD 203 en EC1	10.2.1.2/01
Chronic toxicity to fish					
71.4%	*Fathead minnow Pimephales promelas*	34d-NOEC 34d-LOEC (reproduction)	43 mg a.s./L 86 mg a.s./L	OECD 210 FIFRA 72-4	8.2.2.2
Acute toxicity to invertebrates					
72.1%	*Daphnia magna*	48h-NOEC (mobility)	not valid	OECD 202	8.2.4.1
Chronic toxicity to invertebrates					
72.1%	*Daphnia magna*	21d-NOEC 21d-LOEC(reproduction) 21d-LC_{50}	67 mg a.s./L 160 mg a.s./L > 160 mg a.s./L	FIFRA 72-1	8.2.5.1
Toxicity algae					
72.1%	*Chlorella vulgaris*	72h-EC_{50}	20.9 mg a.s./L	OECD 201	8.2.6.1
71.9%	*Selenastrum capricornutum*	120h-EC_{50}	> 1.4 mg a.s./L	FIFRA 122-2 en 122-3	8.2.6.2
71.9%	*Anabaena flos aquae*	120h-EC_{50}	> 1.8 mg a.s./L	FIFRA 122-2 en 122-3	8.2.6.3
	Navicula pelliculosa	120h- EC_{50}	> 1.5 mg a.s./L	FIFRA 122-2 en 122-3	8.2.6.4
71.4%	Pseudokirchneriella subcapitata	72h-EC_{50}	7.1 mg a.s./L	OECD 201	8.2.6

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Purity	Species	Endpoint	Toxicity value	Test Guideline	Reference no.
71.9%	*Lemna gibba*	14d-EC_{50} 14d NOEC	> 1.6 mg a.s./L < 0.10 mg a.s./L	FIFRA 122-2 en 122-3	8.2.8.1
484 g Ethephon/L (EXP03725A)	*Scenedesmus subspicatus*	72h-EC_{50}	56 mg product/L	OECD 201 en EC C.3	10.2.1.2/02

Toxicity sediment-dwelling organisms
Not provided and not required (21d-NOEC *Daphnia magna* > 0.1 mg a.s./L)

Microcosm or mesocosm tests
Not provided

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

Acute TERs for Ethephon from spray drift at 1 and 3 m.

Crop	% drift	LC/EC_{50} (µg a.s./L)				Initial PECsw actual	TER			
		Higher plants	Fish	Daphnia	Algae	(µg a.s./L)	Daphnia	Fish	Higher plants	Algae
cereals	2.77	> 1600	> 100000	>160000*	> 1400	4.43	>36117	> 22573	> 361	> 316

*21-day LC_{50} of > 160 mg/L used for acute risk assessment (48h acute toxicity study on *D. magna* not valid).

Long-term TERs for Ethephon assuming constant exposure to the initial PECs.

	distance	drift	NOEC (µg as/L)		Initial PECsw actual	TER	TER
crop	(m)	(%)	Fish	Daphnia	(µg as/L)	Fish	Daphnia
cereals	1	2.77	43000	67000	4.43	9706	15124

Bioconcentration

Bioconcentration factor (BCF) ‡	Log Pow < 3
Annex VI Trigger:for the bioconcentration factor	Not required.
Clearance time (CT_{50}) (CT_{90})	Not required.

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Level of residues (%) in organisms after the 14 day depuration phase	Not required.

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Acute oral toxicity bees	LD_{50} > 116.5 µg a.s./bee
Acute contact toxicity bees	LD_{50} > 100 µg a.s./bee
Acute oral toxicity bumblebees	not available
Acute contact toxicity bumblebees	not available

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Crop	Dose (g a.s./ha)	Oral toxicity		Contact toxicity		Annex IV trigger
		LD_{50} (µg a.s./bee)	hazard quotient	LD_{50} (µg a.s./bee)	hazard quotient	
cereals	480	> 116.5	<4.1	> 100	<4.8	50

Ethephon does not reveal an IGR-related mode of action. Hence, this compound is not expected to pose a risk to honey bee brood. Data on the effects of Ethephon on bee brood is therefore not required.

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

Species	Test type, substrate	Max. recommended test dose (g a.s./ha)	Actual dose tested (g a.s./ha)	Overall effect at respective dose in test
Parasitoids				
Aphidius rhopalosiphi	laboratory, glass plate	480 (cereals)	726	87.2% (mortality) -5.4% (slight increase of parasitation efficiency)
Foliage dwelling predators				
Chrysoperla carnea	laboratory, glass plate	480(cereals)	726	-3.4% (less mortality than in the control) 60.1% reduction in reproduction activity
Ground dwelling predatory species				
Poecilus cupreus	laboratory, sand	480(cereals)	726	0% (mortality) 0% (reproduction)
Predatory mites				
Typhlodromus	laboratory,	480 (cereals)	726	17.7 % (mortality)

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Species	Test type, substrate	Max. recommended test dose (g a.s./ha)	Actual dose tested (g a.s./ha)	Overall effect at respective dose in test
pyri	glass plate			No significant adverse effects on reproduction (R=0.67)
Extended laboratory studies				
Aphidius rhopalosiphi	extended laboratory, barley seedlings	480 (cereals)	1440	0% (mortality) 7.1% (reproduction)
Chrysoperla carnea	extended laboratory, maize leaves	480 (cereals)	726	-4.1% (less mortality than in the control) 1.33% (reproduction)
Typhlodromus pyri	extended laboratory,	480 (cereals)	836	-0.2% (mortality) 17% (reproduction)

* all studies are performed with formulation EXP03725A which is considered comparable to the lead formulation, except the extended laboratory study with *Aphidius rhopalosiphi*, which was conducted with a different formulation likely to be worst case

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

Acute toxicity ‡	14d-LC_{50} > 60 kg a.s./ha
Reproductive toxicity ‡	8w-NOEC for reproduction $\geq$ 200 mg a.s./kg

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

Scenario	Crop	LC_{50} (mg a.s./kg)	PECs (mg a.s./kg)	Acute TER	Annex VI trigger
field crops	wheat/barley	> 200*	0.192	> 1042	10

Scenario	Crop	NOEC (mg a.s./kg)	PECs (mg a.s./kg)	Chronic TER	Annex VI trigger
field crops	wheat/barley	$\geq$ 200	0.192	$\geq$ 1042	5

Because the conversion from kg a.s./ha to mg a.s./kg soil could not be done precisely for the acute endpoint the acute risk is based on the NOEC-value from the chronic study

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

……..	< 25 % effect at day 28 at 2.56 mg a.s./kg d.w.soil (1920 g a.s/ha)

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Effects on other non-target organisms

Non-target plants	Carrot: ER_{50} = 2.35 kg a.s./ha. Corn: NOEC = 2.58 kg a.s./ha. Cucumber: ER_{50} = 3.58 kg a.s./ha. Onion: NOEC = 2.35 kg a.s./ha. Ryegrass: NOEC = 2.35 kg a.s./ha. Oats: NOEC = 2.58 kg a.s./ha. Soybean: ER_{50} = 5.04 kg a.s./ha. Cabbage: ER_{50} = 5.15 kg a.s./ha. Lettuce: ER_{50} = 1.46 kg a.s./ha. Tomato: ER_{50} = 3.25 kg a.s./ha.
Collembola	According to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002 rev 2 final, 17 October 2002), laboratory tests on Collembola reproduction are required for persistent substances (DT_{90} >100 days). Ethephon is non persistent (DT_{90} values derived from field test <66 days, see Section B.8.1.3). A study on the reproduction toxicity of Ethephon to Collembola is therefore not required.

Classification and proposed labelling (Annex IIA, point 10)

with regard to ecotoxicological data	R51/R53	Toxic to aquatic organisms, may cause long term adverse effects in the aquatic environment

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APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

AChE	acetylcholinesterase
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography

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LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MoS	margin of safety
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
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
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
r^2	coefficient of determination
RPE	respiratory protective equipment
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year

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