CONCLUSION ON PESTICIDES PEER REVIEW

efsa JOURNAL

APPROVED: 2 December 2022

doi: 10.2903/j.efsa.2023.7742

Peer review of the pesticide risk assessment of the active substance ethephon

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Abstract

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, the Netherlands and co-rapporteur Member State, the United Kingdom, for the pesticide active substance ethephon are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The conclusions were reached on the basis of the evaluation of the representative use of ethephon as a plant growth regulator on cereals (winter and spring barley, winter and spring wheat, winter rye, winter triticale, spelt, durum wheat). The reliable endpoints appropriate for use in regulatory risk assessment are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are reported where identified.

Keywords: ethephon, peer review, risk assessment, pesticide, plant growth regulator

Requestor: European Commission

Question number: EFSA-Q-2014-00717

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Note/update: This scientific output, approved on 2 December 2022, supersedes the previous output published on 7 June 2006 and updated in 25 September 2008 (EFSA, 2008b).

Declarations of interest: If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

Acknowledgement: EFSA wishes to thank the rapporteur Member State, the Netherlands, for the preparatory work on this scientific output.

Suggested citation: EFSA (European Food Safety Authority), Alvarez F, Arena M, Auteri D, Binaglia M, Castoldi AF, Chiusolo A, Colagiorgi A, Colas M, Crivellente F, De Lentdecker C, De Magistris I, Egsmose M, Fait G, Ferilli F, Gouliarmou V, Nogareda LH, Ippolito A, Istace F, Jarrah S, Kardassi D, Kienzler A, Lanzoni A, Lava R, Leuschner R, Linguadoca A, Lythgo C, Magrans O, Mangas I, Miron I, Molnar T, Padovani L, Panzarea M, Parra Morte JM, Rizzuto S, Serafimova R, Sharp R, Szentes C, Szoradi A, Terron A, Theobald A, Tiramani M, Vianello G and Villamar-Bouza L, 2023. Conclusion on peer review of the pesticide risk assessment of the active substance ethephon. EFSA Journal 2023;21 (1):7742, 28 pp. https://doi.org/10.2903/j.efsa.2023.7742

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.

Summary

Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659, lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Ethephon is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of Regulation (EU) No 844/2012, the rapporteur Member State (RMS), the Netherlands, and co-rapporteur Member State (co-RMS), the United Kingdom, received an application from Bayer CropScience AG, CBW Chemie GmbH Bitterfeld-Wolfen (now Nufarm Europe GmbH) and Société Financière de Pontarlier (SFP) (now Adama) for the renewal of approval of the active substance ethephon.

An initial evaluation of the dossier on ethephon was provided by the RMS in the renewal assessment report (RAR), and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 13 of Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The following conclusions are derived.

The uses of ethephon according to the representative uses as a plant growth regulator on cereals (winter and spring barley, winter and spring wheat, winter rye, winter triticale, spelt, durum wheat), as proposed at EU level result in a sufficient efficacy.

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 formulations for representative uses.

A data gap and issue not finalised were identified in the mammalian toxicology section since analytical method used in the studies being of relevance to derive the acute reference dose (ARfD) and the acute operator exposure level (AAOEL) are not available; it is however acknowledged that this information may not be available due to the studies being old (1970s). The aneugenic potential of the plant metabolite HEPA has not been addressed according to the latest state of the art. With regard to acute operator exposure, it is estimated to exceed the AAOEL for the representative formulations 'Ethephon 480 g/L SL' and 'CA3147 660 SL'. For the formulations 'SFPE 480 SL', acute operator exposure would not exceed the AAOEL if the application rate is limited to the lowest representative application rates in the good agricultural practice (GAP) table of 0.288 or 0.24 kg ethephon/ha. However, for this latest formulation, the application rate needs to be lowered to 0.24 kg ethephon/ha to ensure that resident's (child) exposure does not exceed the AOEL.

With regard to residues in food and feed, for fruit crops, further data are needed to exclude the relevance of conjugates in fruits harvested at longer pre-harvest interval (PHI) than 12 days. Monitoring animal residue definition, as ethephon only, is considered provisional with respect to ruminants, pending confirmation with an acceptable metabolism study. For risk assessment of consumption of cereal grains and animal matrices, metabolite HEPA should be considered as a separated component of the residue definition, at least until the potential aneugenic properties are addressed. Assessment of residues in representative uses is sufficiently supported by data except for the use in winter ryes.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses.

In the area of ecotoxicology, the risk to non-target organisms was low. No critical area of concern or issue not finalised was identified.

Ethephon does not meet the ED criteria **for humans** as laid down in point 3.6.5. Regarding **non-target organisms, according to EFSA and RMS, ethephon does not meet the ED criteria according to** Annex II to Regulation (EC) No 1107/2009. However, for some MSs, the uncertainties related to the assessment do not allow to conclude on whether the criteria are met or not.

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Background

Commission Implementing Regulation (EU) No 844/2012[1], as amended by Commission Implementing Regulation (EU) No 2018/1659[2] (hereinafter referred to as 'the Regulation'), lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009[3]. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of an additional 3 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3). Furthermore, in accordance with Article 13(3a), where the information available in the dossier is not sufficient to conclude the assessment on whether the approval criteria for endocrine disruption are met, additional information can be requested to be submitted in a period of minimum 3 months, not exceeding 30 months, depending on the type of information requested.

In accordance with Article 1 of the Regulation, the RMS, the Netherlands, and co-RMS, the United Kingdom, received an application from Bayer CropScience AG, CBW Chemie GmbH Bitterfeld-Wolfen (now Nufarm Europe GmbH) and Société Financière de Pontarlier (SFP) (now Adama) for the renewal of approval of the active substance ethephon. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (the United Kingdom), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on ethephon in the RAR, which was received by EFSA on 2 August 2017 (Netherlands, 2017).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Bayer CropScience AG, CBW Chemie GmbH Bitterfeld-Wolfen (now Nufarm Europe GmbH) and Société Financière de Pontarlier (SFP) (now Adama), for consultation and comments on 16 March 2018. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 16 May 2018. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicants were invited to respond to the comments in column 3 of the reporting table. The comments and the applicants' response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicants in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA, the RMS on 5 July 2018. On the basis of the comments received, the applicants' response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicants, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table.

[1] Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, pp. 26–32.

[2] Commission Implementing Regulation (EU) No 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine-disrupting properties introduced by Regulation (EU) 2018/605.

[3] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, pp. 1–50.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

In addition, following a consultation with Member States (TC 203, January 2019), it was considered necessary to apply an additional clock stop of 20 months in accordance with Commission Implementing Regulation (EU) No 2018/1659, to be able to conclude whether the approval criteria for endocrine disruption (ED) in line with the scientific criteria for the determination of endocrine-disrupting properties, as laid down in Commission Regulation (EU) 2018/605[4], are met.

A consultation with the RMS on the conclusions arising from the peer review of the risk assessment except the ED part took place in April 2021. A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in October–November 2022.

A key supporting document to this conclusion is the peer review report (EFSA, 2022), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

A list of the relevant end points for the active substance and the formulation is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for ethephon according to Annex II of Regulation (EC) No 1107/2009 are summarised in Appendix A.

A key supporting document to this conclusion is the peer review report (EFSA, 2022), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting tables (23 July 2018);
- the evaluation table (9 November 2022);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (The Netherlands, 2022), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion and its background documents would not be accepted to support any registration outside the EU for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulation for representative uses

Ethephon is the name for 2-chloroethylphosphonic acid (IUPAC). There is no ISO common name for this substance.

The formulations for the representative uses for the evaluation were 'Ethephon 480 g/L SL', 'SPFE 04 (ORMET/BAIA E)', both soluble concentrates (SL) containing 480 g/L ethephon and 'CA3147' 660 SL, a soluble concentrate (SL) containing 660 g/L ethephon.

The representative uses evaluated were spray applications as plant growth regulator to increase resistance to lodging through straw shortening and strengthening in cereals (winter and spring barley, winter and spring wheat, winter rye, winter triticale, spelt, durum wheat) in the EU. Full details of the GAPs can be found in the list of end points in Appendix B.

Data were submitted to conclude that the representative uses of ethephon proposed at EU level result in a sufficient plant growth regulatory effect, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014).

[4] Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. OJ L 101, 20.4.2018, pp. 33–36.

Conclusions of the evaluation

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

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

The proposed minimum purity specifications for ethephon are based on batch data from industrial scale production and, for impurities, on quality control data too. Ethephon is manufactured as a technical concentrate (TK). There was not an agreement between the applicants on a common specification. The specification of the active substance as manufactured is 692–735 g/kg for BayerCropScience AG, 730–775 g/kg for CBW Chemie GmbH Bitterfeld-Wolfen and 720–745 g/kg for Société Financière de Pontarlier, respectively. The theoretical minimum purity on dry weight basis is 910 g/kg for all sources. 1,2-dichloroethane and 2-chloroethanol were considered relevant impurities with maximum limits of 0.3 g/kg for both substances. Based on the renewal data and the changes in the relevant impurity profile (see Section 2), it is proposed to update the reference specification based on the data from the Bayer AG source. The batches used in the (eco)toxicological assessment support the proposed reference specification (see Sections 2 and 5). Sources of CBW Chemie GmbH Bitterfeld-Wolfen and Société Financière de Pontarlier, were considered equivalent to the proposed reference specification (see Sections 2 and 5).

FAO specifications for the TC and TK under the old procedure are available (AGP:CP/ 367, 2000) with a minimum content of ethephon in the TC of 910 g/kg (373/TC/S/F) and the content of the relevant impurities mono 2-chloroethyl ester, 2-chloroethyl phosphonic acid (MEPHA) and 1,2-dichloroethane of maximum 20 and 0.5 g/kg, respectively.

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

Adequate methods are available for the generation of pre-approval data required for the risk assessment. Methods of analysis are available for the determination of the active substance and relevant impurities in the technical material and in the representative formulations.

The residue definition for monitoring in plant matrices was defined as ethephon and its conjugates, expressed as ethephon for cereal grain and straw and as ethephon for the other matrices. Various methods based on LC–MS/MS were proposed by the applicants for enforcement of the components of the residue definition in the different matrices with limits of quantification (LOQs) of 0.01 mg/kg expressed as ethephon in all commodity groups. A data gap was identified for the applicant SFP for an analytical method, a sufficient extraction procedure and ILV including a hydrolysis step in cereals. A data gap was identified for the applicant CBW to demonstrate sufficient efficiency of the extraction procedure (hydrolysis) for monitoring residues in cereal grain and straw (relevant for CBW).

LC–MS/MS methods exist for monitoring the residues of ethephon in animal matrices with LOQs of 0.01 mg/kg (Bayer CropScience AG and CBW Chemie GmbH Bitterfeld-Wolfen) and 0.005 mg/kg (Société Financière de Pontarlier) in milk, egg, meat, fat and liver.

Appropriate LC–MS/MS methods were proposed by the applicants for monitoring ethephon in the environmental matrices. The different LOQs for the determination of ethephon in soil, water and air can be seen in the list of endpoints. LC–MS/MS methods exist to monitor ethephon in soil up to a LOQ of 0.005 mg/kg, in water up to an LOQ of 0.05 μg/L and in air with an LOQ of 1.4 $\mu g/m^3$.

Monitoring ethephon in body fluids is possible with LC–MS/MS method with an LOQ of 0.05 mg/L.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on dermal absorption (EFSA PPR Panel, 2012), Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products (EFSA, 2014b) and Guidance on the Application of the CLP Criteria (ECHA, 2017).

Ethephon was discussed at the Pesticides Peer Review Experts' Meeting 186 in November 2018 and its endocrine-disrupting properties at the TC 203 in January 2019.

The newly proposed reference specification from the Bayer AG source is covered by the batches used in the toxicity tests, while the current specification is not fully supported by these batches. The reference specifications from the two other sources (CBW Chemie GmbH Bitterfeld-Wolfen and Société Financière de Pontarlier) are considered equivalent from a toxicological point of view to the Bayer source, which represents a more complete toxicological dossier. Two impurities are toxicologically relevant based on their harmonised classification according to Regulation (EC) No 1272/2008 (CLP Regulation)[5], 1,2-dichloroethane due to its classification as Carc cat 1B, H350 'may cause cancer' and 2-chloroethanol that present a higher acute toxicity than ethephon (Acute Tox. 2, H300 'Fatal if swallowed', Acute Tox. 1, H310 'Fatal in contact with skin' and Acute Tox. 2, H330 'Fatal if inhaled'). At the levels specified in the newly proposed reference specification, these impurities do not represent a concern. Regarding the impurity MEPHA that is identified as a relevant impurity in the FAO specification, likely due to its degradation product, 2-chloroacetic acid, that is acutely more toxic than ethephon (Acute Tox. 3, H301 'Toxic if swallowed', Acute Tox 3, H311 'Toxic if inhaled' *inter alia*), its own toxicological profile would not require this impurity to be considered relevant. For most impurities present in either reference specification, sufficient toxicological information can be retrieved from publicly available sources, such as ECHA's website,[6] showing that they do not impact on the toxicological profile of the technical material. For other significant impurities, QSAR analysis did not indicate a toxicological relevance; however, the predictions were of low reliability.

The analytical method used in the 90-day toxicity study in dog study used as a basis to derive the acceptable daily intake (ADI) and acceptable operator exposure level (AOEL) is correctly validated. Regarding other endpoints, the respective analytical method could not be retrieved, such as the rat multigeneration, rabbit developmental toxicity and human volunteer studies (data gap). Regarding the human volunteer studies, although of relevance to derive the acute reference dose (ARfD) and the acute operator exposure level (AAOEL) (see below on the derivation of ref values from human studies), it is acknowledged that analytical methods may not be available due to the studies being old (1970s) (data gap and issue not finalised).

In rat, ethephon is rapidly and extensively absorbed after oral administration, it is widely distributed, poorly metabolised – 2-hydroxyethephon (HEPA) being identified as a minor metabolite – and mainly excreted via the urine and as ethylene through exhaled air. A residue definition for body fluids and tissues is established as ethephon alone.

An *in vitro* interspecies comparative metabolism study including rat, dog and human S9 liver fractions did not evidence the occurrence of any unique human metabolite.

Ethephon is considered harmful after acute oral and inhalation administration, and toxic after acute dermal exposure; its strong acidic properties (pH < 2) lead to being corrosive for the skin, eyes and respiratory tract, and inconclusive with regard to its skin sensitisation properties. The resulting harmonised classification regarding acute toxicity being established as Acute Tox 4, H302, Acute Tox 3, H311, Acute Tox 4, H332, Skin Corr. 1B, H314 and EUH071 'corrosive to the respiratory tract' according to the CLP Regulation (ATP[7]). Ethephon does not absorb light above 290 nm and, therefore, no phototoxicity or photomutagenicity studies are required.

The main effect following short-term repeated oral and dermal administration of ethephon was the inhibition of cholinesterase (ChE) activity. Erythrocyte ChE inhibition was the most relevant effect in all studies. The dog was considered the most sensitive species and the relevant no observed adverse effect level (NOAEL) of 2 mg/kg body weight (bw) per day for erythrocyte ChE inhibition was derived taking into consideration both the 90-day and 2-year dog studies and was used to set the ADI and the AOEL.

Based on an up-to-date genotoxicity data package, the overall weight of evidence was sufficient to conclude that ethephon is unlikely to be genotoxic. Erythrocyte ChE inhibition was the most sensitive toxicological endpoint upon long-term exposure in rats and mice with respective NOAELs established at 13 and 4.5 mg/kg bw per day, respectively; no test substance-related carcinogenic effects were observed up to 1,416 and 1,477 mg/kg bw per day in rats and mice, respectively, leading to the conclusion that ethephon is unlikely to pose a carcinogenic hazard to humans.

[5] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, pp. 1–1355.

[6] https://echa.europa.eu.

[7] Commission Regulation (EU) No 605/2014 of 5 June 2014 amending, for the purposes of introducing hazard and precautionary statements in the Croatian language and its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures. OJ L 167, 6.6.2014, 36–49.

In several generational reproductive toxicity studies in rats, none of them performed according to the most up-to-date protocol (OECD, 2001), no adverse effects were observed on reproduction or fertility up to 137 mg/kg bw per day and no offspring effects were observed up to the highest dose level tested of 137 mg/kg bw per day. The NOAEL for parental toxicity was set at 14 mg/kg bw per day based on erythrocyte ChE inhibition. In another two-generation study, doses tested were 0, 23, 231, 2,444 mg/kg bw per day. In this study, decreased litter weight and pup survival were seen at 2,444 mg/kg bw per day; therefore, in this study, an offspring NOAEL of 231 mg/kg bw per day was set; no adverse effects on the reproduction were observed up to 2,444 mg/kg bw per day.

In developmental toxicity studies in rat and rabbit where ChE inhibition was not measured, no signs of maternal or developmental toxicity were observed in rats up to 500 mg/kg bw per day and no signs of developmental toxicity were observed in rabbits up to 150 mg/kg bw per day; maternal toxicity in rabbits included clinical signs and reduced pregnancy rate with an NOAEL of 50 mg/kg bw per day.

No signs of delayed neurotoxicity were observed in hens and no signs of neurotoxicity were seen in repeated-dose toxicity studies. Although some inhibition of brain ChE inhibition occurred, the magnitude of the inhibition was not considered adverse, remaining erythrocytes ChE inhibition the most sensitive parameter for cholinesterase activity. There were no effects on the thyroid system and pups were not more sensitive than adults for the most sensitive endpoints. Accordingly, it was agreed to waive the need for submitting a developmental neurotoxicity study for ethephon. Ethephon did not impair the immunological response in a 28-day immunotoxicity study in mice up to 1,373 mg/kg bw per day.

Three subacute studies on human volunteers were submitted. An overall NOAEL of 0.5 mg/kg bw per day was established based on clinical observations (urination, diarrhoea, bowel movements) at 1.5 mg/kg bw per day. Although the individual studies were old (1970s) and of limited quality (see data gap and issue not finalised above), they were considered as relevant evidence for the derivation of the acute toxicological reference values (ARfD and AAOEL). It should be noted that in general, the reference values shall be based on animal studies and human studies should not performed or used in the pesticides risk assessment.

The **ADI** and **AOEL** of ethephon are 0.02 mg/kg bw per day based on the NOAEL of 2 mg/kg bw per day for ChE inhibition in the 90-day and 2-year oral studies in dog and applying an uncertainty factor (UF) of 100; no correction being needed with regard to oral absorption to derive the AOEL.[8] The ADI and AOEL previously set were 0.03 mg/kg bw per day based on the 1-year dog study supported by human data (European Commission, 2008). An UF of 1000 was used, including an extra factor of 10 since ChE activity was not measured in the dog study; this study is now considered of limited acceptability. The 90-day and 2-year dog studies were not available in the Annex I original dossier.

The **ARfD** and **AAOEL** are 0.05 mg/kg bw based on the NOAEL of 0.5 mg/kg bw per day for clinical observations in human volunteer studies and applying an UF of 10; no correction being needed with regard to oral absorption to derive the AAOEL. The previously set ARfD (post Annex I inclusion, European Commission, 2008) was the same value, based on a 28-day study in dogs and supported by human volunteer studies. Taking into account that in the dog study, AChE inhibition was observed only after 14 days of treatment, dogs were concluded not to present acute effects.[9] The overall NOAEL of 0.5 mg/kg bw per day based on clinical observations from the human volunteer studies was considered for the derivation of acute TRVs: by applying an interhuman variability UF of 10, an ARfD of the same value of the previous, 0.05 mg/kg bw per day, was derived. Acute effects in laboratory animals were observed at considerably higher doses; for instance, a lowest observable adverse effect level (LOAEL) of 500 mg/kg bw acute neurotoxicity study in rats. During the meeting,[8] it was noted that according to the pesticide legislation,[3] human studies shall not be performed or used in the pesticides risk assessment; in particular, approval criteria for active substances provided for in Article 4, point 6, of Regulation (EC) No 1107/2009 states: *'In relation to human health, no data collected on humans shall be used to lower the safety margins resulting from tests or studies on animals'*. In the case of ethephon, the decision to use existing human data, albeit old and of limited quality, as point of departure to derive the ARfD and AAOEL was considered appropriate as more conservative.

The ethephon dossier contains three representative formulations, Ethephon 480 SL, a soluble concentrate (SL) formulation containing 480 g ethephon/L, CA3147 660 SL, an SL formulation, containing a nominal 660 g ethephon/L and SFPE 480 SL, an SL formulation containing 480 g ethephon/L. For the first two formulations, based on *in vivo* rat and *in vitro* rat and human skin studies, dermal absorption was set at 93% for the concentrate formulations (a higher value compared to default values justified by the corrosive properties of these formulations) and 5% for the in-use spray dilutions; 5%

[8] Refer to experts' consultation 2.4 in the Report of Pesticides Peer Review Experts' Meeting 186 (EFSA, 2022).
[9] Refer to experts' consultation 4.2 in the Report of Pesticides Peer Review Experts' Meeting 186 and TC 203 in (EFSA, 2022).

dermal absorption was also considered appropriate for the risk assessment of worker, residents' and bystanders' exposure. Regarding SFPE formulation, 14% dermal absorption for the concentrate and 43% for the in-use spray dilution were derived from an *in vitro* study on human skin.

With regard to the representative uses in cereals, tractor-mounted equipment, acute operator exposure to Ethephon 480 SL (Bayer) and CA3147 660 SL (CBW) exceeds the AAOEL, even considering the use of personal protective equipment (PPE) and lower application rate as proposed in the GAP table (0.36 and 0.33 kg a.s./ha, respectively). Acute operator exposure to SFPE 480 SL (SPF) also exceeds the AAOEL at the higher representative application rate (0.48 kg a.s./ha), even considering the use of PPE. Considering the lower application rates in the GAP table of 0.24–0.288 kg a.s./ha, the use of PPE (such as gloves, hood and visor during mixing and loading and gloves during application) would ensure that operator exposure does not exceed the AAOEL.

An assessment of exposure to Ethephon 480 SL using water soluble bag formulations presented by the RMS, but not considered in the GAP table, together with the use of PPE – gloves during mixing, loading and application – would however ensure that operator exposure does not exceed the AAOEL. Similarly, a safe use would be reached for SPFE 480 SL by using water soluble bags with the use of PPE (gloves, hood and visor during mixing and loading and gloves during application, EFSA, 2014b).

Worker exposure is estimated to remain below the AOEL for the formulations Ethephon 480 SL and CA3147 660 SL even when no PPE are worn, however, regarding the SFPE 480 SL formulation, worker exposure is estimated to remain below the AOEL (87% of the AOEL) only for a maximum application rate of 0.288 kg ethephon/ha, when workers use protective clothing.

Residents' exposure is estimated to remain below the AOEL for the formulations Ethephon 480 SL and CA3147 660 SL and below the AAOEL for bystanders. Regarding the SFPE 480 SL formulation, bystander (child) exposure is estimated to remain below the AAOEL only when drift reduction equipment is used during application, and resident's exposure (child) is estimated to remain below the AOEL (97% of the AOEL) only when drift reduction equipment is used during application and for a maximum application rate of 0.24 kg a.s./ha (the lowest representative application rate in the GAP table for spring barley uses).

Toxicological data have been provided on the metabolite 2-hydroxyethyl phosphonic acid **HEPA,** a minor metabolite observed in rat studies. The metabolite was found to be of lower acute and repeated-dose oral toxicity than the parent ethephon, not sharing its potential for ChE inhibition. The metabolite was concluded as unlikely to be genotoxic during the peer review, i.e. does not produce gene mutation or chromosome aberrations; however, EFSA notes that its aneugenic potential has not been addressed according to the latest scientific state of the art (EFSA PPR panel, 2020) – criteria not available at the time of the dossier submission or ongoing peer review (data gap).

3. Residues

The assessment in the residue section is based on the OECD guidance document on overview of residue chemistry studies (OECD, 2009), the OECD publication on maximum residue level (MRL) calculations (OECD, 2011), the European Commission guideline document on MRL setting (European Commission, 2011) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

Ethephon was discussed at the Pesticides Peer Review Experts' Meeting 187 in November 2018.

Plant metabolism studies with radiolabelled ethephon on wheat, tomatoes and pineapple were submitted for the previous EU review. Metabolism studies on wheat and tomatoes are considered valid. No conclusion can be drawn from the study in pineapple. In addition, a reliable metabolism study in cotton has been submitted in the renewal dossier. Supplementary information from published articles was available on the fate of ethephon after application to squash, cucumber, apple and cherry trees. Metabolism of ethephon in plants mainly proceeds via conversion to 2-hydroxyethyl phosphonic acid (HEPA) and via decomposition to ethylene, and phosphate. As the representative use is on cereals, the plant metabolism study on wheat is the most relevant. This study shows that in the edible part (grain) of cereals treated at normal field rate, ethephon (including its conjugates) and the metabolite HEPA are present at similar levels. In tomatoes, ethephon is the main residue component, with HEPA being present > 0.15 mg eq/kg (above 10% TRR). Conjugates do not contribute significantly to the residue in tomato fruits. In cotton, parent ethephon comprised the main part of the residues in both the gin trash and cotton seed, metabolite HEPA being present at significant lower levels.

Taking into account the toxicological profile of metabolite HEPA available at the time of the meeting and the low levels found in residues trials, the experts' peer review meeting agreed that the residue

definition for risk assessment to be ethephon, free and conjugated, for cereals, pulses and oilseeds.[10] For fruit crops, the residue definition for risk assessment was proposed to be ethephon only (without conjugates) for short PHI (up to 12 days), but further data will be needed to exclude the relevance of conjugates in fruits harvested at longer PHI than 12 days. With respect to residue definition for monitoring, the meeting agreed for cereals to be ethephon free and conjugates and for fruit crops, pulses and oilseed ethephon alone. The same residue definitions could be applied to rotational crops since no additional persistent metabolites have been identified to be formed in soil. However, since a data gap has been identified by toxicology (see Section 2) to address the potential aneugenic properties of HEPA, EFSA proposes that for risk assessment, also metabolite HEPA should be considered as a separated component of the residue definition (due to different toxicological properties), at least until the potential aneugenic properties of HEPA are addressed.

Ethephon levels appeared to be relatively stable during pasteurisation, whereas during baking, boiling, brewing and sterilisation, ethephon is mainly degraded to ethylene.

Livestock metabolism studies in poultry were presented for the previous EU review and are considered acceptable under current guidelines. Considering these studies and data on residues found in poultry commodities, ethephon can be proposed for the monitoring residue definition in poultry. For risk assessment of animal matrices, also metabolite HEPA (major in cereal grains) should be considered as a separated component of the residue definition (due to different toxicological properties), at least until the potential aneugenic properties of HEPA are addressed. A metabolism in lactating goats was also previously submitted, but after revaluation, it is not any longer considered acceptable (data gap). Animal monitoring and risk assessment residue definition are considered provisional with respect to ruminants as ethephon, pending confirmation with an acceptable metabolism study with lactating ruminants.

Ethephon is not a fat-soluble substance and metabolism in fish is not triggered.

As regards the representative uses in cereals (barley, wheat, triticale, rye, spelt, durum wheat), there are seven residue trials in NEU and seven residue trials in SEU that support the GAP proposed by Bayer for barley and eight residue trials in NEU and eight residue trials in SEU that support the GAP proposed by Bayer for wheat.

In addition, two residue trials are considered to support the GAP of CBW Chemie for rye, provided it is confirmed that the analytical method encompasses the conjugates of ethephon (data gap). None of the other residue trials provided by CBW Chemie and SFP are considered acceptable to support the corresponding GAPs in cereals, however these GAPs may be considered covered by the available residue trials except for the use in winter rye (CBW Chemie data gap).

All the acceptable trials are supported by storage stability data and validated analytical methods and no change of MRL is considered necessary on base of these data (see Appendix B). In order to consider CBW trials, the final report on the additional storage stability study with conjugated residues in cereal commodities needs to be provided (data gap). Residues in pollen and bee products are not expected based on the representative uses.

A number of acceptable processing trials were also available; therefore, processing factors were proposed for wheat and barley processed products (see Appendix B).

A rotational crop study was submitted for the first evaluation with ethephon on radishes, collards and wheat. The study is considered to be acceptable under the current standards. In plant extracts, no radioactive peaks greater than 0.01 mg/kg were detected. The radioactivity found in plant matrices was attributable to incorporation into all categories of biomolecules. Following application of ethephon according to the GAP on cereals, no quantifiable residues are expected in following crops.

Based on the representative uses evaluated and the livestock data submitted, residues of ethephon are expected to occur in edible animal matrices. The observed levels are covered by existing MRLs. However, MRLs should be considered provisional as residue definition for ruminants is pending and acceptable metabolism study.

The overall consumer risk assessment was conducted by using EFSA Pesticide Residues Intake Model (PRIMo) rev 3.1 and it covers the residues of ethephon used in barley and wheat following the Bayer CropScience GAPs. The chronic (theoretical maximum daily intake (TMDI)) was calculated for maximum 23.2% of ADI (PRIMo 2) or 19% of ADI (PRIMo 3.1) and the acute consumer intakes (IESTI) accounted for 14.4% ARfD (wheat, same result with PRIMo rev 2 and PRIMo rev 3.1) being lower for the other representative crops. MRLs were assessed for outdoor uses in barley and wheat. Since only seven trials in NEU and seven trials in SEU were available for barley extrapolation was done from residue trials in wheat (application takes place before forming of the edible part). Therefore,

[10] Refer to experts' consultation 3.2 in the Report of Pesticides Peer Review Experts' Meeting 187 (EFSA, 2022).

these two representative uses are sufficiently supported by residue trials validated by the analytical method and storage stability studies and MRLs proposals have been derived (see the detailed assessment in the Appendix A). For animal commodities, no new MRLs are required, since existing MRLs are sufficient. Nevertheless, consumer risk assessment should be considered provisional until data gap on aneugenic properties of HEPA is addressed and the metabolite HEPA is appropriately considered in the risk assessment.

4. Environmental fate and behaviour

Ethephon was discussed at the Pesticides Peer Review Meeting TC 198 in November 2018.

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, ethephon exhibited low to moderate persistence, forming the major (> 10% applied radioactivity (AR)) metabolite **ethylene** (max. 91% AR in the volatile traps after 1–180 days), which exhibited very low to low persistence. Mineralisation to carbon dioxide accounted for 5.7%–22.3% AR after 30–44 days. The formation of unextractable residues accounted for 11%–34% AR after 21–30 days. In anaerobic soil incubations, ethephon showed a rapid degradation forming the major metabolite ethylene up to 94% AR after 30 days. Degradation of ethephon in soil is slightly enhanced by irradiation, forming the major metabolite **HEPA** (max 10.6% AR at 10 days in the irradiated experiment). When dosed in soil laboratory incubations in the dark, HEPA exhibited very low to low persistence. The soil adsorption properties of ethephon were investigated in four soils, ranging in pH from 4.6 to 6.0, where ethephon exhibited low to slight mobility in soil. Due to the lack of reliable data for sorption behaviour at soil pH values above 6, the experts of the Pesticides Peer Review Meeting TC 198 agreed that a default K_{Foc} value of 10 L/kg (1/n = 1) can be used as a worst case to simulate neutral and alkaline systems and should be used in the risk assessment. Metabolite HEPA can be considered to exhibit low mobility or to be immobile in soil. It was concluded that the adsorption of HEPA was not pH dependent. In satisfactory field dissipation studies carried out at 11 sites (three sites in the Unites States, two sites in Germany, two sites in the UK, two sites in Italy and two sites in Spain), ethephon exhibited low to moderate persistence. Sample analyses were only carried out for the parent ethephon. Except for the US trials, field study DT50 values were accepted as being reasonable estimates of degradation and were normalised to FOCUS reference conditions (20°C and pF2 soil moisture) using the time step normalisation procedure in accordance with FOCUS (2006) kinetics guidance and following the EFSA (2014a) DegT50 guidance for those trials not tailored for $DegT_{50\ matrix}$ determination. The field data endpoints were combined with laboratory values to derive modelling endpoints.

In laboratory incubations in dark aerobic natural sediment water systems, ethephon was rapidly degraded to ethylene (max. ca. 100% AR recovered from the volatile traps). Additionally, metabolite 'component E' was observed at ≥ 5% (max 5.35%) of applied radioactivity at two subsequent sampling times. The experts of the Peer Review Meeting TC 198 agreed that no further assessment of this metabolite is needed, although a precautionary conservative risk assessment is presented in this conclusion. The unextractable sediment fraction accounted for 1.5%–4.5% AR after 3–14 days. Mineralisation accounted for only 0%–2.3% AR at the end of the study (7–30 days). All water/sediment studies were done in high pH water systems (pH water phase 6.8–8.9). Therefore, in the absence of information on degradation of ethephon in acidic aquatic systems, for modelling purposes, the peer review agreed to use a default half-life value in water and sediment of 1,000 days for ethephon for systems in which the pH is lower than 7. The rate of decline of ethephon in a laboratory sterile aqueous photolysis experiment was slow relative to that occurred in the aerobic sediment water incubations. No chromatographically resolved component (excluding ethephon) accounted for > 7.4% AR. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for ethephon and metabolites HEPA and 'Component E' using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 2.1 or version 3.2 of the Steps 1–2 in FOCUS calculator).

The necessary groundwater exposure assessments were appropriately carried out for ethephon and metabolite HEPA using FOCUS (European Commission, 2014) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4.[11] The potential for groundwater exposure from the representative uses by ethephon above the parametric drinking water limit of 0.1 μg/L was concluded to be low in

[11] Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008a) and Walker equation coefficient of 0.7.

geoclimatic situations that are represented by all the pertinent FOCUS groundwater scenarios for acidic soils. In neutral and alkaline soils, the 80th percentile of the mean annual leachate concentration at 1 m soil depth, PEC_{gw} values for ethephon are > 0.1 μg/L in the following situations:

- Winter cereals (early application at 1 × 480 g a.s./ha): three out of nine FOCUS scenarios, max 0.133 μg/L (neutral/alkaline soils, Okehampton scenario, PELMO model) with absolute application dates.
- Winter cereals (late application at 1 × 480 g a.s./ha): two out of nine FOCUS scenarios, max 0.147 μg/L (neutral/alkaline soils, Jokioinen scenario, PELMO model) with absolute application dates.
- Winter cereals (early application at 1 × 726 g a.s./ha): four out of nine FOCUS scenarios, max 0.185 μg/L (neutral/alkaline soils, Kremsmuenster scenario, PEARL model) with absolute application dates.
- Winter cereals (late application at 1 × 726 g a.s./ha): four out of nine FOCUS scenarios, max 0.210 μg/L (neutral/alkaline soils, Kremsmuenster scenario, PEARL model) with absolute application dates.
- Spring cereals (early application at 1 × 360 g a.s./ha): two out of six FOCUS scenarios, max 0.116 μg/L (neutral/alkaline soils, Hamburg scenario, PEARL model) with absolute application dates; one out of six FOCUS scenarios, 0.137 μg/L (neutral/alkaline soils, Hamburg scenario, PEARL model) with fixed application date.

The PEC_{gw} levels of metabolite HEPA were in the range < 0.001–0.021 μg/L.

The applicant provided appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater is abstracted for drinking water. The conclusion of this consideration was that neither ethephon nor any of its degradation products that trigger assessment (HEPA) would be expected to undergo any substantial transformation due to oxidation at the disinfection stage of usual water treatment processes.

The atmospheric half-life estimated with the Atkinson model (EPIWIN v. 3.10 software) for ethephon (10.2 days) gives an indication that when applied as a spray, aerosols formed at the time of spraying may have the potential to be subject to long range transport to areas where it has not been used, via the atmosphere (FOCUS, 2008). However, as ethephon is not persistent in soil and in the water sediment system, it does not fulfil the POP (Persistent Organic Pollutant) criteria laid out in Regulation 1107/2009. Taking into consideration that ethylene is an active substance and that was measured at a maximum of 94% and 101% of applied ethephon from aerobic soil and water/sediment systems, respectively, the behaviour in air of metabolite ethylene and potential for local and global effects was addressed. It was concluded that the expected contribution of ethylene in air as a result of the application of ethephon is negligible compared to the contribution of other (natural and industrial) sources.

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix B. A key to the persistence and mobility class wording used, relating these words to numerical DT and Koc endpoint values can be found in Appendix C.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013).

Ethephon has been discussed by the experts in ecotoxicology during the Pesticides Peer Review Experts' Meeting 188 in November 2018 and a consecutive ad hoc consultation in November 2020.

The batches used in the ecotoxicity studies are considered representative of the proposed technical specification except for the ED studies on NTOs (data gap).

The representative formulations of ethephon are Ethephon 480 SL, SFPE 04480 SL and CA3147 660 SL. In some cases, a different formulation than the representative ones was used in the ecotoxicological toxicity tests. However, based on all the available information, bridging between all the formulations used in the ecotoxicity test and the three representative formulations was supported.

Acute and long-term oral toxicity data for **birds and mammals** were available with the active substance ethephon. The long-term toxicity endpoints for birds and mammals were discussed and agreed in the experts' meeting and in a consecutive ad hoc consultation.[12]

[12] Experts' consultation 5.1 and 5.2 of the Report of the Pesticides Peer Review Experts' Meeting 188 (27–29 November 2018).

Based on the data and risk assessment available, low acute and long-term risk from dietary exposure to **birds** was concluded at Tier 1 for all the representative uses.

A low acute and long-term risk from dietary exposure to ethephon was also indicated for **mammals** for all the representative uses.

The risk to birds and mammals from consumption of contaminated water was low. A risk assessment from secondary poisoning was not triggered.

Acute toxicity data were available with the major plant metabolite of ethephon, HEPA and mammals. No toxicity data were available for birds and 10 times higher toxicity than the parent was assumed in assessing the risk to birds from this metabolite, resulting in a low acute risk. The long-term risk to HEPA was considered to be addressed by the available risk assessments for the parent as ethephon rapidly degrades into HEPA in plants.

Sufficient acute and chronic toxicity studies were conducted with **aquatic organisms** (fish, aquatic invertebrates,[13] algae and aquatic macrophytes) for the active substance ethephon, and the representative formulations.

Based on the available data and risk assessments, a low acute and chronic risk to **fish, aquatic invertebrates, algae** and **aquatic macrophytes** was concluded at (FOCUS) Step1/2 for all the representative uses of ethephon.

Toxicity data were not available with the surface water metabolite HEPA and aquatic organisms, except for aquatic plants (*Lemna*), and a risk assessment was conducted assuming that the metabolite is 10 times of higher toxicity than the parent. Based on this, the acute and chronic risk to aquatic organisms from HEPA was assessed to be low.

Sufficient acute (oral and contact) toxicity data were available with adult **honey bees**, ethephon and the formulations for representative uses. Sufficient data on chronic toxicity to adult honey bees from ethephon were also available.[14]

For honey bee larvae, there were reliable 4-day (single and multiple dose) toxicity data with ethephon, but did not cover all stages of larval development, i.e. 22 days.[15] There were also higher tier tests where bee-brood development was studied. A bee brood-feeding test was available that indicated potential effects on brood. In addition, a tunnel test of more realistic exposure than the bee-brood test was available with honey bees to flowering *Phacelia* indicating that toxicity decreases with increasing ageing time of residues without adverse effects on adult or bee brood. The overall data were deemed in a weight of evidence to address the effects on larvae, considering also that it was indicated that the pupa is not the most sensitive bee life stage.[14] Considering this, the endpoint of the multiple-dose larvae study was used in a Tier-1 risk assessment of bee larvae.

The risk to honeybees was assessed in accordance with the guidance document of European Commission (2002a) and a low acute risk to adult honey bees via oral and contact exposure to ethephon was indicated for all the representative uses.

The risk to honeybees was also assessed in accordance with the EFSA Guidance document (2013) and a low risk to adult (acute oral, acute contact and chronic) honey bees and honey bee larvae (chronic oral) was concluded (at screening and Tier 1) for all representative uses.

Data on the assessment of sublethal effects on honeybees (hypopharyngeal glands (HPG)) were available with ethephon and a low risk was indicated based on the EFSA Guidance document (2013).

An assessment for the accumulative toxicity was not performed.

A low acute and chronic risk to (adult and larvae) honeybees from exposure to residues of ethephon in surface water was indicated. Based on the available information and a screening assessment, a high acute and chronic risk to (adult and larvae) honeybees for exposure to residues of ethephon in guttation fluids could not be excluded. An assessment of the exposure via residues in puddle water was not available.

The major plant metabolite of ethephon, HEPA, is present in the edible plant parts (wheat grain). Toxicity data were not provided to address the risk to bees from exposure to HEPA (data gap). Based on worst-case assumptions and assessment, high risk from exposure of bees to HEPA could not be excluded for the applications of CA3147 660SL.

Acute oral and contact toxicity data were available for adult bumblebees. Risk assessment in accordance with the EFSA Guidance document (2013) was conducted for ethephon. Based on these, a low acute contact risk to adult bumblebees was concluded.

[13] Experts' consultation 5.3 of the Report of the Pesticides Peer Review Experts' Meeting 188 (27–29 November 2018).
[14] Experts' consultation 5.5 of the Report of the Pesticides Peer Review Experts' Meeting 188 (27–29 November 2018).
[15] Experts' consultation 5.4 of the Report of the Pesticides Peer Review Experts' Meeting 188 (27–29 November 2018).

No data were available for solitary bees.

For **non-target terrestrial arthropods**, first-tier toxicity data with the two standard test species *Typhlodromus pyri* and *Aphidius ropalosiphi* and two additional species (*Orius laevigatus* and *Poecilus cupreus*) were available with the representative formulation Ethephon 480SL.

Extended laboratory studies with aged residues for the two standard test species (*T. pyri* and *A. ropalosiphi*) and three additional species (*Chrysoperla carnea, Aleochara bilineata* and *Coccinella septempunctata*) were also available with the representative formulations.

Based on the available data and risk assessments, low in-field and off-field risk to non-target terrestrial arthropods (at Tier 1) was concluded for all the representative uses.

The risk to **earthworms** and other **soil macro-organisms**, **soil microorganisms**, as well as **non-target terrestrial plants** and **biological processes in sewage treatment plants** was assessed as low for all the representative uses.

6. Endocrine disruption properties

With regard to the assessment of the endocrine disruption (ED) potential of ethephon for humans according to the ECHA/EFSA guidance (2018), in determining whether ethephon interacts with the oestrogen, androgen and steroidogenesis (EAS) and thyroid (T)-mediated pathways, the number and type of effects induced and the magnitude and pattern of responses observed across studies were considered. Additionally, the conditions under which effects occur were considered; in particular, whether or not endocrine-related responses occurred at dose(s) that also resulted in overt toxicity. The assessment is therefore providing a weight-of-evidence analysis of the potential interaction of ethephon with the EAS and T signalling pathways using the available evidence in the data set.

For the EAS-T modalities, the data set is complete, and no adversity has been observed. Therefore, in line with ECHA/EFSA guidance (2018), scenario 1a is applicable and ethephon is not considered to meet the ED criteria as laid down in point 3.6.5 **for humans** of Annex II to Regulation (EC) No 1107/ 2009.

The outcome of the assessment reported above for humans also applies to **wild mammals as non-target organisms**.

For non-target organisms other than mammals, a Xenopus Eleutheroembryonic Thyroid Assay (XETA) was available for the T-modality, as well as a Rapid Oestrogen Activity In Vivo (REACTIV) assay, a Rapid Androgen Disruption Adverse-outcome Reporter (RADAR) assay and a Fish Short-Term Reproduction Assay (FSTRA) assay for the EAS modalities. All the available data were discussed in the Peer Review experts' meeting TC 88. In particular, the relevance of the studies for their use in the ED assessment (i.e. choice of the tested concentration, suitability to sufficiently investigate the endocrine activity) and their reliability were discussed. Overall, the choice of the tested concentration and the related maximum tolerated concentration (MTC) was considered appropriate (see experts' consultation 5.7–5.10 of the meeting report, EFSA, 2022).

For the T-modality, no T-related endocrine activity was detected in the available XETA. However, ethephon was found to be weakly positive in a ToxCast assay, the thyroperoxidase (TPO) inhibition assay (NCCT_TPO_AUR_dn). Therefore, in line with Annex A of the ECHA/EFSA Guidance (2018), the relevance of such a test to sufficiently investigate T-mediated endocrine activity was discussed at the experts' meeting TC 88 (EFSA, 2022). Overall, by considering all the available data in the weight of evidence and the remaining uncertainties (see table below), the experts agreed that it is unlikely that ethephon meets the ED criteria for the T-modality for non-mammalian species.

Regarding the EAS-modalities, the reliability of the RADAR and the REACTIV assays was discussed at the expert meeting.[16] Based on the evidence provided by the embryo assays, an FSTRA was performed to further explore EAS-mediated activity. In this study, some changes in both males and females were observed in the gonad histopathology and gonadal staging. A slight decrease in fecundity was also observed at the highest tested dose. However, the changes in gonad histopathology were not so prominent and the interpretation of those is not so univocal (see experts' consultation 5.10 of the meeting report). Most experts in the meeting (TC 88) considered that the available evidence did not allow a clear conclusion and that further data would be needed. On the contrary, EFSA and the RMS are of the opinion that the weight of evidence and the analysis of the uncertainties (see uncertainty analysis below) are not suggesting a convincing pattern of endocrine activity.

[16] Refer to experts' consultation 5.8–5.9 in the Report of Pesticides Peer Review Experts' Meeting 88 (EFSA, 2022).

Line of evidence	Uncertainty	Comment
T-modality		
Negative XETA	The XETA is negative, but the XETA might not be suitable to conclude on T-mediated endocrine activity of Ethephon, since the XETA might not be a suitable assay for substance that are TPO inhibitors (see Annex A of the ECHA/EFSA Guidance, 2018).	Ethephon is positive in the AUR_TPO assays; however, the effect is seen only at the highest tested dose of 30 μM. This concentration is equivalent to ~4 mg/L at cellular level which is considered difficult to be reached. The available graphs extractable from Toxcast show that Etephon is a weak TPO inhibitor compared to other TPO inhibitors.
Criteria not met for mammals and humans	Potential difference in physiology and sensitivity between mammals and non-mammalian species.	All the T-mediated parameters in all the available studies in mammals did not show any change compared to the control. The data set was considered sufficiently investigated and negative. No evidence related to a potential TPO inhibition was available. Although there may be some physiological differences, it is also well known that the endocrine system is well conserved across vertebrates.
EAS-modality		
Equivocal REACTIV	The REACTIV is a non-validated test method for which a draft OECD Guideline is not yet available. No clear validity criteria are therefore available. The results were equivocal.	When applying the validity criteria of other assays with eleutheroembryos, the test does not meet 2 of the validity criteria used by the RMS. The RMS considered the results equivocal for anti-estrogenicity and requested an FSTRA to clear any potential concern.
Negative RADAR	The RADAR was overall negative. However, one of the validity criteria was not met.	During the expert meeting, it was considered that while the assay is reliable for anti-androgenicity, it should be considered not reliable for androgenicity as one of the validity criteria is not met.
FSTRA	Changes in the gonad histopathology of both sexes.	Those findings were both normal physiological findings which, however, in the case of ethephon seem to be exacerbated by the exposure to the chemical when compared to control. Moreover, ethephon showed evidence of anti-estrogenicity in the REACTIV, although the test is only considered supportive. It is noted that animals exposed during sexual maturation may be more sensitive to anti estrogenic compound. It is also noted that a reduction in fecundity was observed at the high concentration which may be the consequence of the histopathological changes.
Criteria not met for mammals and humans	Potential difference in physiology and sensitivity between mammals and non-mammalian species.	A number of in vivo data and the complete battery for sufficiently investigating the endocrine activity was available. No positive findings were observed. Although there may be some physiological differences, it is also well known that the endocrine system is well conserved across vertebrates.
Possible Mode of Action (MoA)	A mode of action was not postulated	Based on the available data (change in gonad histopathology and slight decrease in fecundity), it is not possible to postulate a plausible mode of action, as data informing on molecular initiating events (ToxCast ER assays and model, AR assays, steroidogenesis and aromatase inhibition assays; OECD 456 (steroidogenesis); OECD 458 (ARTA); OPPTS 890.1200 (aromatase); OECD 441 (Hershberger) and earlier Key events (e.g. VTG level) are available and negative.

Based on the above considerations, ethephon is not considered to meet the ED criteria as laid down in point 3.6.5 **for humans**. Regarding **non-target organisms, according to EFSA and**

RMS, ethephon does not meet the ED criteria according to Annex II to Regulation (EC) No 1107/2009. However, for some MSs, the uncertainties related to the assessment do not allow to conclude on whether the criteria are met or not.

7. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

Compound (name and/or code)	Ecotoxicology
Ethephon	Low risk to soil organisms
HEPA	Low risk to soil organisms

Table 2: Groundwater[a]

Compound (name and/or code)	> 0.1 µg/L at 1 m depth for the representative uses[b]	Biological (pesticidal) activity/ relevance	Hazard identified	Consumer RA triggered	Human health relevance
	Step 2	Step 3a.	Steps 3b. and 3c.	Steps 4 and 5	
Ethephon	Acidic soils: no Neutral/alkaline soils: < 0.001–0.21 µg/L (less than half of the relevant FOCUS scenarios > 0.1 µg/L)	Yes	–	Yes	Yes
HEPA	No	No	No[c], not triggered	Open	Assessment not required; of lower acute and repeated-dose toxicity than the parent; aneugenic potential has not been addressed according to the latest state of the art

(a): Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).
(b): FOCUS scenarios or relevant lysimeter. Ranges indicated for FOCUS scenarios include the result from the model giving the highest concentration at each scenario, as needed to comply with European Commission (2014) guidance.
(c): The metabolite was concluded as unlikely to be genotoxic i.e. does not produce gene mutation or chromosome aberrations; however, its aneugenic potential has not been addressed.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Ethephon	Low risk to aquatic organisms
HEPA	Low risk to aquatic organisms

Table 4: Air

Compound (name and/ or code)	Toxicology
Ethephon	Rat LC_{50} inhalation = 3.26 mg/L air/4 h whole body – Acute Tox 4 – H332 'Harmful if inhaled'; EUH071 'Corrosive to the respiratory tract'[a]
Ethylene	STOT SE 3 – H336 'May cause drowsiness or dizziness'[a]

(a): Harmonised classification according to CLP Regulation.

8. Particular conditions proposed to be taken into account by risk managers

Risk mitigation measures (RMMs) identified following consideration of Member State (MS) and/or applicant's proposal(s) during the peer review, if any, are presented in this section. These measures applicable for human health and/or the environment leading to a reduction of exposure levels of operators, workers, bystanders/residents, environmental compartments and/or non-target organisms for the representative uses are listed below. The list may also cover any RMMs as appropriate, leading to an acceptable level of risks for the respective non-target organisms.

It is noted that final decisions on the need of RMMs to ensure the safe use of the plant protection product containing the concerned active substance will be taken by risk managers during the decision-making phase. Consideration of the validity and appropriateness of the RMMs remains the responsibility of MSs at product authorisation, taking into account their specific agricultural, plant health and environmental conditions at national level (Table 5).

Table 5: Risk mitigation measures proposed for the representative uses assessed

Representative use	Cereals (Ethephon 480 SL)	Cereals (CA3147 660 SL)	Cereal (SFPE 480 SL)		
Application rate	0.48 kg a.s./ha	0.726 kg a.s./ha	0.24 kg a.s./ha	0.288 kg a.s./ha	0.48 kg a.s./ha
Operator risk	Use of PPE is required[(a),(b)]	Use of PPE is required[(a),(b)]	Use of PPE is required[(c)]	Use of PPE is required[(c)]	Use of PPE is required[(a),(b)]
Worker exposure	–	–	Use of PPE is required[(d),(e)]	Use of PPE is required[(d)]	> AOEL
Bystander exposure	–	–	Drift reduction equipment is required during application	Drift reduction equipment is required during application	Drift reduction equipment is required during application
Resident exposure	–	–	Drift reduction equipment is required during application	> AOEL	> AOEL
Risk to aquatic organisms	–	–	–		–

(a): For tractor-mounted applications: gloves during mixing, loading and application (EFSA, 2014b).
(b): Water soluble bags formulations presented by the RMS but not proposed in the GAP table.
(c): For tractor-mounted applications: gloves, hood and visor during mixing and loading and gloves during application (EFSA, 2014b).
(d): Protecting clothing (workwear).
(e): Not calculated, extrapolated from the next column (0.288 kg a.s./ha).

9. Concerns and related data gaps

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for one or more of the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[17] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

[17] Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, pp. 127–175.

The following issues or assessments that could not be finalised have been identified, together with the reasons including the associated data gaps where relevant, which are reported directly under the specific issue to which they are related:

1) Analytical method used in the human volunteer studies of relevance to derive the acute reference dose (ARfD) and the acute operator exposure level (AAOEL) (see Section 2).

   a) Analytical method used in the rat multigeneration, rabbit developmental toxicity and human volunteer studies, the latest being of relevance to derive the acute reference dose (ARfD) and the acute operator exposure level (AAOEL). Regarding the human volunteer studies, it is acknowledged that this information may not be available due to the studies being old (1970's) (relevant for all representative uses evaluated; see Section 2).

9.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29 (6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at the lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

The following critical areas of concern are identified, together with any associated data gaps, where relevant, which are reported directly under the specific critical area of concern to which they are related:

Critical areas of concern were not identified.

9.3. Overview of the concerns identified for each representative use considered (Table 6)

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 6.)

Table 6: Overview of concerns reflecting the issues not finalised, critical areas of concerns and the risks identified that may be applicable for some but not for all uses or risk assessment scenarios

Representative use		Ethephon 480 SL cereals appl. rate 0.48 kg a.s./ha	CA3147 660 SL cereals appl. rate 0.726 kg a.s./ha	SFPE 480 SL cereals appl. rate 0.48 kg a.s./ha	SFPE 480 SL cereals appl. rate 0.288 kg a.s./ha	SFPE 480 SL cereals appl. rate 0.24 kg a.s./ha
Operator risk[(c)]	Risk identified	X	X	X		
	Assessment not finalised					
Worker risk	Risk identified			X		
	Assessment not finalised					

Representative use		Ethephon 480 SL cereals appl. rate 0.48 kg a.s./ha	CA3147 660 SL cereals appl. rate 0.726 kg a.s./ha	SFPE 480 SL cereals appl. rate 0.48 kg a.s./ha	SFPE 480 SL cereals appl. rate 0.288 kg a.s./ha	SFPE 480 SL cereals appl. rate 0.24 kg a.s./ha
Resident/ bystander risk	Risk identified			X	X	
	Assessment not finalised					
Consumer risk	Risk identified					
	Assessment not finalised					
Risk to wild non-target terrestrial vertebrates	Risk identified					
	Assessment not finalised					
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified					
	Assessment not finalised					
Risk to aquatic organisms	Risk identified					
	Assessment not finalised					
Groundwater exposure to active substance	Legal parametric value breached					
	Assessment not finalised					
Groundwater exposure to metabolites	Legal parametric value breached[(a)]					
	Parametric value of 10 μg/L[(b)] breached					
	Assessment not finalised					

The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–7 for further information.

(a): Based on classification made in the context of this evaluation procedure under Regulation (EC) No 1107/2009. It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.

(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission (2003).

(c): Acute operator exposure exceeds the AAOEL if the product applied is not formulated as water soluble bags as proposed by the RMS; however, this type of formulation is not part of the representative uses proposed by the applicants. In alternative for one of the representative formulations (SFPE 480 SL), acute operator exposure would not exceed the AAOEL if the application rate is limited to the lowest representative application rates in the GAP table of 0.288 and 0.24 kg ethephon/ha. However, for this latest formulation, the application rate needs to be lowered to 0.24 kg ethephon/ha to ensure that resident's (child) exposure does not exceed the AOEL (see Section 2).

10. List of other outstanding issues

Remaining data gaps not leading to critical areas of concern or issues not finalised but considered necessary to comply with the data requirements, and which are relevant for some or all of the representative uses assessed at EU level. Although not critical, these data gaps may lead to uncertainties in the assessment and are considered relevant.

These data gaps refer only to the representative uses assessed and are listed in the order of the sections:

- Analytical method, a sufficient extraction procedure and ILV including a hydrolysis step for the determination of the compounds of the residue definition for cereal grain and straw (relevant for applicant SFP; see Section 1).

- Data to demonstrate sufficient efficiency of the extraction procedure (hydrolysis) for monitoring residues in cereal grain and straw (relevant for applicant CBW; see Section 1).
- Aneugenic potential of the metabolite HEPA has not been addressed according to the latest state of the art (relevant for all representative uses evaluated; see Sections 2 and 3).
- A new metabolism study in lactating ruminants (goats) according to current guidelines. (relevant for all representative uses evaluated; see Section 3).
- Applicant CBW need to submit sufficient residue trials to support the GAP of the representative use in winter rye with an analytical method that encompasses the quantification of conjugated ethephon (relevant for CBW representative use in winter rye; see Section 3).
- Toxicity data to address the risk to bees from exposure to HEPA (relevant for all representative uses evaluated; see Section 5).
- Information on the compositions of the batches used in the ED studies on NTOs was not available for comparison with the reported specifications (relevant for all representative uses evaluated; see Section 5).

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Abbreviations

1/n	slope of Freundlich isotherm
λ	Wavelength
ε	decadic molar extinction coefficient

a.s.	active substance
AAOEL	acute acceptable operator exposure level
AChE	Acetylcholinesterase
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
AR	androgen receptor
ARfD	acute reference dose
ATP	Adaptation to Technical Progress
bw	body weight
ChE	cholinesterase
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
dw	dry weight
EAS	oestrogen, androgen and steroidogenesis modalities
ECHA	European Chemicals Agency
EEC	European Economic Community
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FSTRA	Fish Short-Term Reproduction Assay
GAP	Good Agricultural Practice
HPG	hypopharyngeal glands
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{doc}	organic carbon linear adsorption coefficient
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC–MS	liquid chromatography–mass spectrometry
LC–MS-MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
mm	millimetre (also used for mean measured concentrations)
MRL	maximum residue level
MS	mass spectrometry
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
Pa	pascal
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PHI	preharvest interval
PPE	personal protective equipment
ppm	parts per million (10^{-6})
QSAR	quantitative structure–activity relationship
r^2	coefficient of determination
RAR	Renewal Assessment Report
$t_{1/2}$	half-life (define method of estimation)

TC	Technical material
TER	toxicity exposure ratio
TER_A	toxicity exposure ratio for acute exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TK	technical concentrate
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
UF	uncertainty factor
WHO	World Health Organization

Appendix A – Consideration of cut-off criteria for ethephon according to Annex II of Regulation (EC) No 1107/2009 of the European Parliament and of the Council

Properties		Conclusion
CMR[(a)]	Carcinogenicity (C)	No evidence of carcinogenic potential for ethephon
	Mutagenicity (M)	No evidence of genotoxic potential for ethephon
	Toxic for Reproduction (R)	No evidence of reproductive toxicity potential for ethephon
Endocrine-disrupting properties		Ethephon is not considered to meet the criteria for endocrine disruption for human health and non-target organisms according to points 3.6.5 and 3.8.2 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605.
POP	**Persistence**	Ethephon is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Long-range transport	
PBT	**Persistence**	Ethephon not considered to be a persistent, bioaccumulative and toxic (PBT) substance according to point 3.7.2 of Annex II of Regulation (EC) 1,107/2009.
	Bioaccumulation	
	Toxicity	
vPvB	**Persistence**	Ethephon not considered to be a very persistent, very bioaccumulative substance according to point 3.7.3 of Annex II of Regulation (EC) 1,107/2009.
	Bioaccumulation	

(a): ECHA (2012); ATP 06 (Commission Regulation (EU) No 605/2014 of 5 June 2014 amending, for the purposes of introducing hazard and precautionary statements in the Croatian language and its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures. OJ L 167, 6.6.2014, pp. 36–49).

Appendix B – List of end points for the active substance and the representative formulation

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.7742

Appendix C – Wording EFSA used in Section 4 of this conclusion, in relation to DT and Koc 'classes' exhibited by each compound assessed

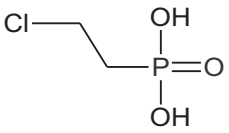
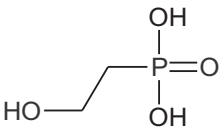
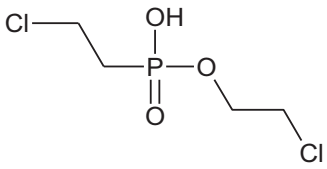
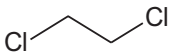
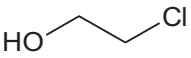
Wording	DT_{50} normalised to 20°C for laboratory incubations[(a)] or not normalised DT_{50} for field studies (SFO equivalent, when biphasic, the DT_{90} was divided by 3.32 to estimate the DT50 when deciding on the wording to use)
Very low persistence	< 1 day
Low persistence	1 to < 10 days
Moderate persistence	10 to < 60 days
Medium persistence	60 to < 100 days
High persistence	100 days to < 1 year
Very high persistence	A year or more

Note these classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.
(a): For laboratory soil incubations, normalisation was also to field capacity soil moisture (pF2/10 kPa). For laboratory sediment water system incubations, the whole system DT values were used.

Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2,000
Slight mobility	2,001–5,000
immobile	> 5,000

Based on McCall et al. (1980).

Appendix D – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
Ethephon	2-chloroethylphosphonic acid ClCCP(=O)(O)O UDPGUMQDCGORJQ-UHFFFAOYSA-N	
HEPA	2-hydroxyethylphosphonic acid OCCP(=O)(O)O SEHJHHHUIGULEI-UHFFFAOYSA-N	
MEPHA mono 2-chloroethyl ester, 2-chloroethyl phosphonic acid	2-chloroethyl hydrogen (2-chloroethyl)phosphonate O=P(O)(CCCl)OCCCl NLAFDAIUYHCRGU-UHFFFAOYSA-N	
1,2-dichloroethane	1,2-dichloroethane ClCCCl WSLDOOZREJYCGB-UHFFFAOYSA-N	
2-chloroethanol	2-chloroethanol ClCCO SZIFAVKTNFCBPC-UHFFFAOYSA-N	

(a): The compound name in bold is the name used in the conclusion.
(b): ACD/Name 2018.2.2 ACD/Labs 2018 Release (File version N50E41, Build 103230, 21 July 2018).
(c): ACD/ChemSketch 2018.2.2 ACD/Labs 2018 Release (File version C60H41, Build 106041, 7 December 2018).