CONCLUSION ON PESTICIDES PEER REVIEW

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

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State France and co-rapporteur Member State Estonia for the pesticide active substance fosetyl are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative uses of fosetyl as a fungicide on grapes, citrus and pome fruits. The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

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Keywords: fosetyl, fosetyl-Al, peer review, risk assessment, pesticide, fungicide, bactericide

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Update: This scientific output, approved on 24 May 2018, supersedes the previous output published on 18 January 2006 and updated on 12 June 2013 (EFSA, 2006).

Amendment: A corrigendum was issued because following some comments received after finalisation of the EFSA conclusion, additional considerations appeared necessary regarding the maternal NOAEL from the rabbit developmental study and it was concluded that neither an ARfD nor an AAOEL should be set.

The correction affects the Section on mammalian toxicology and the Section on residues where the acute consumer risk assessment has been deleted as considered obsolete. Similar changes have been made in the respective parts of the List of endpoints (Appendix A). In addition, two data gaps related to the physical/chemical properties of the formulation have been removed, however the latter does not materially affect the outcome of the risk assessment. To avoid confusion, the older version has been removed from the EFSA Journal, but is available on request, as is a version showing all the changes made.

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Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') 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. Fosetyl is one of the active substances listed in Regulation (EU) No 686/2012. EFSA finalised a previous conclusion on fosetyl on 14 December 2005.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), France, and co-rapporteur Member State (co-RMS), Estonia, received an application from Bayer CropScience AG, Fosetyl-Al Annex I Renewal Iberica Task Force (FAIRITF, composed by Industrias Afrasa, S.A., SAPEC Agro, S.A., Cheminova Agro S.A., Probelte S.A.U., and Proplan Plant Protection Company, SL), OXON SAE Fosetyl Task Force (composed by Oxon Italia SpA and Sumi Agro Europe Limited) for the renewal of approval of the active substance fosetyl. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Estonia), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on fosetyl in the renewal assessment report (RAR), which was received by EFSA on 12 April 2017. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Bayer CropScience AG, FAIRITF, and OXON SAE Fosetyl Task Force, for comments on 12 July 2017. 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 13 September 2017.

Following consideration of the comments received on the RAR, 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 and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether fosetyl can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative use of fosetyl as a fungicide on grapes, citrus and pome fruits, as proposed by the applicants. Full details of the representative uses can be found in Appendix A of this report.

Data were submitted to conclude that the representative uses of fosetyl-aluminium proposed at the European Union (EU) level result in a sufficient fungicidal and bactericidal efficacy.

A data gap was identified for a detailed reporting of the scientific peer-reviewed open literature on the active substance and its relevant metabolites dealing with side effects on human health.

In the area of identity, physical and chemical properties and analytical methods, data gaps were identified for additional validation data for several monitoring methods and Independent Laboratory Validation (ILV) methods for residues in water and soil.

In the mammalian toxicology section, the technical specification for one applicant is not covered by the toxicological batches and the toxicity profile of some impurities is missing. The developmental neurotoxicity study available on aluminium should be provided and pending its analysis, further data might be requested for fosetyl-Al. Moreover, data gaps are set to provide further clarification regarding the involvement of parathyroid hormones in the hypothesised mode of action of fosetyl-Al and level 2/3 studies to conclude on the endocrine disruptor potential of fosetyl-Al. Finally, an exceedance of the reference value is concluded for workers exposed to aluminium as a metabolite (assessment included for informative purpose).

In the residue section, the consumer dietary risk assessment cannot be finalised considering the data gaps identified for a complete residue data set on oranges compliant with the critical southern Europe (SEU) Good Agricultural Practice (GAP) (FAIRITF), for a complete residue data set on grapes and compliant with the critical SEU GAP (FAIRITF) and for four additional residue trials on grapes and compliant respectively with the northern Europe (NEU) and SEU GAPs to complete the residue data set (OXON SAE Fosetyl Task Force). Valid storage stability data on citrus fruit covering the maximum storage time period of the residues from the trials on oranges and mandarins are also requested (FAIRITF). No chronic intake concern was identified using the maximum residue level (MRL) proposals for the representative uses (theoretical maximum daily intake (TMDI): 73% of acceptable daily intake (ADI), German child). Since pome fruit and grapes can be visited for pollen and nectar collection and treatment can take place at flowering, residues of fosetyl-Al and phosphonic acid in pollen and bee products for human consumption cannot be excluded and further information is requested.

The data available on environmental fate and behaviour were sufficient to carry out the required environmental exposure assessments at EU level, with the notable exception that a data gap was identified for information on the effect of water treatment processes on the nature of residues of both the active substance and its identified metabolites potentially present in surface water, when surface water is abstracted for drinking water. This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses. Another data gap was identified for reliable field DT_{50} and DT_{90} estimates from three different field trial sites for phosphonic acid, and for monitoring data.

In the area of ecotoxicology, the technical specification for one applicant is not covered by the ecotoxicological batches. A data gap was identified for further information to address the risk to aquatic organisms for phosphonic acid. In addition, data gaps were identified to perform the risk assessment for honeybees. Finally, further information is needed to address the risk to non-target terrestrial plants.

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Background

Commission Implementing Regulation (EU) No 844/2012[1] (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[2]. 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).

In accordance with Article 1 of the Regulation, the RMS France and co-RMS Estonia received an application from Bayer CropScience AG, Fosetyl-Al Annex I Renewal Iberica Task Force (FAIRITF, composed by Industrias Afrasa, S.A., SAPEC Agro, S.A., Cheminova Agro S.A., Probelte S.A.U., and Proplan Plant Protection Company, SL), OXON SAE Fosetyl Task Force (composed by Oxon Italia SpA and Sumi Agro Europe Limited) for the renewal of approval of the active substance fosetyl. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Estonia), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on fosetyl in the RAR, which was received by EFSA on 12 April 2017 (France, 2017).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Bayer CropScience AG, FAIRITF, and OXON SAE Fosetyl Task Force, for consultation and comments on 12 July 2017. 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 13 September 2017. 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 and the RMS on 23 October 2017. 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, 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.

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.

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 April–May 2018.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative uses of fosetyl

[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, p. 26–32.

[2] 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, p. 1–50.

as a fungicide and bactericide on grape, citrus and pome fruits, as proposed by the applicants. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2018), 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 October 2017);
- the evaluation tables (23 May 2018);
- 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 (France, 2018), 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 report and its background documents would not be accepted to support any registration outside the European Union (EU) for which the applicants has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Fosetyl is the ISO common name for ethyl hydrogen phosphonate (IUPAC). Fosetyl-aluminium, a variant of fosetyl, is the modified ISO common name for aluminium tris(ethyl phosphonate) (IUPAC).

It should be noted that the evaluation was based on data belonging to the variant fosetyl-aluminium.

The representative formulated products for the evaluation were 'Fosetyl-aluminium (FEA) + Fluopicolide (FLC) WG 71.11', a water-dispersible granule (WG) containing 666.7 g/kg fosetyl-aluminium and 44.4 g/kg fluopicolide; 'Fosetyl-aluminium (FEA) WG 80', a WG containing 800 g/kg fosetyl-aluminium; 'Fosetyl-Al 80% WP', a wettable powder (WP) containing 800 g/kg fosetyl-aluminium and 'SIP40958', a WG containing 300 g/kg fosetyl-aluminium, 160 g/kg copper (as copper oxychloride) and 28.5 g/kg cymoxanil.

The representative uses evaluated were spray applications for the control of *Plasmopara viticola* in grapes in the EU, to control *Phytophthora* spp. in citrus in southern EU and spray applications to control *Phytophthora* spp. and *Erwinia amylovora* in pome fruits in the EU. Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the representative uses of fosetyl-aluminium proposed at EU level result in a sufficient fungicidal and bactericidal efficacy, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014).

A data gap has been identified for a detailed reporting of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on human health (e.g. input parameters, key words, relevance/reliability used by all the applicants are missing in the RAR) and published within the 10 years before the date of submission of the dossier, to be conducted and clearly reported in the RAR in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011).

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, 2012a) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

The proposed specifications for fosetyl-aluminium are based on batch data from industrial scale production and in one case on quality control data, too. There was not an agreement between the applicants on a common specification of the technical materials. The minimum purity of the active substance as manufactured is 960 g/kg for Bayer CropScience AG, 970 g/kg for Cheminova Agro S.A.-Probelte-Proplan, 965 g/kg for Industrias Afrasa S.A., 960 g/kg for SAPEC Agro S.A. and 965 and 974 g/kg for Oxon Italia SpA and Sumi Agro Europe limited sources respectively. EFSA disagrees on having individual specifications of an active substance originating from the same applicant. A FAO specification under the new procedure is available (384.013/TC, January 2013) with a minimum content of fosetyl-aluminium of 960 g/kg, belonging to the technical materials of Bayer CropScience AG and SAPEC Agro S.A.

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 fosetyl-aluminium or the representative formulations. The main data regarding the identity of fosetyl-aluminium and its physical and chemical properties are given in Appendix A.

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 in the technical material and in the representative formulations.

The residue definition for monitoring in plant matrices was defined as sum of fosetyl, phosphonic acid and their salts, expressed as phosphonic acid. Various methods based on liquid chromatography with tandem mass spectrometry (LC–MS/MS) were proposed by the applicants for enforcement of the components of the residue definition in the different matrices. The proposed methods are determining fosetyl and phosphonic acid individually, but the limit of quantifications (LOQs) are expressed as fosetyl-aluminium and phosphonic acid respectively. The quick method for the analysis of numerous highly polar pesticides in foods of plant origin (QuPPe) with LC–MS/MS can be used for the determination of fosetyl in all commodity groups with a LOQ of 0.01 mg/kg expressed as fosetyl-aluminium; however, no Independent Laboratory Validation (ILV) is available. The LOQ for phosphonic acid is 0.1 mg/kg in high water, dry and acidic commodities and of 0.5 mg/kg in high oil content commodities. The task forces submitted also LC–MS/MS methods for monitoring with LOQs of 0.01 and 0.05 mg/kg for all matrices.

LC–MS/MS methods were proposed by all applicants for monitoring the compounds of the residue definition in animal matrices. The different LOQs for the determination of fosetyl (expressed as fosetyl-aluminium) and phosphonic acid can be seen in the list of endpoints.

Appropriate LC–MS/MS methods exist for monitoring fosetyl and phosphonic acid in soil. Fosetyl can be determined with LOQs of 0.025 and 0.05 mg/kg expressed as fosetyl-aluminium and phosphonic acid can be measured with LOQs of 0.025 and 0.2 mg/kg. A data gap was identified for applicant Oxon SAE Fosetyl Task force for an analytical method for the determination of phosphonic acid in soil with a LOQ of 0.05 mg/kg.

Fosetyl can be monitored in surface, ground and drinking water by LC–MS/MS with LOQs of 0.05 and 0.1 μg/L expressed as fosetyl-aluminium, while phosphonic acid with LOQ of 0.1 μg/L. Data gaps were identified, however, for additional validation data of the ILV method for the determination of residues of phosphonic acid in drinking water relevant for FAIRITF, and for an analytical method for the determination of phosphonic acid in drinking water with an LOQ of 0.1 μg/L and its ILV relevant for Oxon SAE Fosetyl Task force.

Residues of fosetyl in air can be determined by LC–MS/MS methods with LOQs of 3 $\mu g/m^3$ and 0.1 mg/m^3, or by gas chromatography with flame ionisation detector (GC-FID) with a LOQ of 0.1 mg/m^3, all expressed as fosetyl-aluminium.

Monitoring fosetyl and phosphonic acid in body fluids is possible with LC–MS/MS methods with LOQs of 0.05 mg/L expressed as fosetyl-aluminium and phosphonic acid respectively.

2. Mammalian toxicity

The toxicological profile of the active substance fosetyl-Al and its metabolites was discussed at the Pesticides Peer Review teleconference 165 and assessed based on the following guidance documents: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012a) and Guidance on dermal absorption (EFSA PPR Panel, 2012).

To assess the toxicological profile of the active substance, the applicant submitted a complete set of valid toxicity studies. The technical specification for one applicant is not covered by the toxicological batches and the toxicity profile of some impurities is missing (data gap). For the other applicants, the

batches used in the toxicity studies were concluded as being representative of new technical specifications for the active substance and no relevant impurities have been identified.

In the toxicokinetic studies, fosetyl-Al is rapidly and totally absorbed within 24 h. Fosetyl-Al is widely distributed mainly in liver, kidney, fat, adrenal glands, skin, gonads, lungs and spleen. It is rapidly metabolised in CO_2 excreted via exhaled air and phosphonates eliminated in urine (parent also detected). Ethanol has also been detected. The faeces are the main route of excretion in case of repeated administrations. A comparative *in vitro* metabolism study has been submitted and no metabolism has been observed in human or rat liver microsomes (the results suggest that the hydrolysis of the active substance *in vivo* is abiotic or via esterases not located in liver microsomes).

In the acute toxicity studies, fosetyl-Al shows a low toxicity by oral, dermal and inhalation routes. It is neither a skin irritant nor skin sensitiser. However, it is classified as Eye Dam.1 H318 (causes serious eye damage)[3] and now proposed to be classified as Eye Irrit. 2 H319 (causes serious eye irritation)[4] based on new studies allowing the assessment of effects' reversibility. A phototoxicity study is not required as its molar extinction/absorption coefficient is less than 10 $L \times mol^{-1} \times cm^{-1}$ at wavelengths above 290 nm.

In short-term toxicity studies, fosetyl-Al does not induce adverse effects up to the highest dose levels in the mouse and rat by oral or dermal administration. Therefore, a no-observed-adverse-effect level (NOAEL) of 1,196 mg/kg body weight (bw) per day has been determined in an oral 90-day study in rat. In a similar study in dog, a NOAEL of 274 mg/kg bw per day has been set based on decreased absolute weight gonads and prostate in males. This value is considered the overall short-term NOAEL. In addition, a NOAEL of 500 mg/kg bw per day has been derived from a 90-day oral rat study aiming to assess the mode of action of the adverse effects observed in the long-term study. This NOAEL is based on an increase of calcium levels in urine and related changes in the urinary bladder (calculi, hyperplasia), kidney (functional alterations and histopathological changes) and ureters (dilatation).

Fosetyl-Al is unlikely to be genotoxic based on previously submitted tests for the first inclusion and new battery of tests submitted for the renewal of the approval of the substance. Negative results are reported in the Ames test, *in vitro* mammalian cell gene mutation tests, chromosome aberration tests and *in vivo* micronucleus studies in mice. A photomutagenicity study is not required as the substance does not absorb light between 190 and 800 nm.

No new study was submitted to assess the long-term toxicity and carcinogenicity potential of fosetyl-Al. Studies in mouse, rat and dog and two additional mechanistic studies in rat are available. Mice do not show any treatment-related effect up to very high dose levels (3,956 mg/kg bw per day). In the 2-year rat study, the NOAEL for chronic and carcinogenic effects is set at 348 mg/kg bw per day based on calculi, hyperplasia and inflammation of the urinary bladder. Transitional cell papilloma and carcinoma are also observed in urinary bladder of the high-dose males group. Based on mechanistic studies, these tumours have not been considered relevant for human as they are related to a chronic irritation mechanism at doses at which humans would not be exposed to. In the 2-year dog study, the NOAEL is 288 mg/kg bw per day based on decreased body weight gain, testicular changes and findings in kidneys in females. Overall, the Member States experts concluded that fosetyl-Al is unlikely to be carcinogenic.

In the multigeneration rat study, the parental NOAEL is 482 mg/kg bw per day based on decreased body weight during premating period in F2B, the reproductive NOAEL is 954 mg/kg bw per day based on decrease of corpora lutea in F0 and F1B generations. For offspring, a lowest observable adverse effect level (LOAEL) of 482 mg/kg bw per day has been derived as decreased absolute weight of the spleen in F3B generation showing a dose–response relationship is observed from the lowest dose. Three developmental studies in rat and rabbit are available. While in the rat, the maternal and developmental NOAELs are set at 1,000 mg/kg bw per day, in the most recent rabbit study the NOAEL for maternal and developmental toxicity was set at 100 mg/kg bw per day based on decreased body weight gain observed during the first days of dosing and on increased incidence of dilated ureter, respectively. Following some comments received after finalisation of the EFSA conclusion, additional considerations appeared necessary regarding the maternal NOAEL from the rabbit developmental study. Therefore, this NOAEL was re-discussed in Pesticides Peer Review Experts Meeting 190 and the maternal NOAEL has been set at 300 mg/kg bw per day (the highest tested dose) as the body weight loss observed at 300 mg/kg bw per day was confirmed to be attributed to one single animal. Fosetyl-Al is concluded as unlikely to be teratogenic.

[3] 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, p. 1–1355.

[4] It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.

During the experts' meeting, it has been noted that a published developmental neurotoxicity (DNT) study on aluminium exists, and the experts agreed that pending on the analysis of this study (not available at the moment to the peer review) a DNT for fosetyl-Al might be requested (data gap).

Fosetyl-Al does not show any evidence of neurotoxic potential based on the standard studies provided and notably on a 90-day rat study including a functional observation battery (FOB).

No evidence of immunotoxic effects are observed in the available data package.

Fosetyl-Al is not classified or proposed to be classified as toxic for reproduction category 2 or carcinogenic category 2, in accordance with the provisions of Regulation (EC) No 1272/2008, and therefore, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met. With regard to the scientific risk assessment, the experts agreed that the involvement of the parathyroid hormones in the hypothesised mode of action of fosetyl-Al should be clarified (data gap). In addition, considering that the sensitive parameters were not measured in the multigeneration study and the effects observed in the multigeneration, 2-year and 90-day studies, the submission of level 2/3 studies according to the OECD conceptual framework (OECD, 2012) is needed to conclude on the endocrine disrupting potential of fosetyl-Al (data gap).

The acceptable daily intake (ADI) and acceptable operator exposure level (AOEL) for fosetyl-Al are 1 mg/kg bw per day based on the developmental NOAEL in rabbit and applying an uncertainty factor (UF) of 100. The acute reference dose (ARfD) and the acute AOEL (AAOEL) for fosetyl-Al are 1 mg/kg bw per day based on the maternal decreased body weight gain observed at the beginning of the dosing in rabbit developmental study and applying an UF of 100. Following the re-discussion of the maternal NOAEL from the rabbit developmental study in Pesticides Peer Review Experts Meeting 190, neither an ARfD nor an AAOEL should be set. No correction for oral absorption is needed. During the first peer review, an ADI of 3 mg/kg bw per day based on the chronic studies and an AOEL of 5 mg/kg bw per day based on mechanistic study were determined. No ARfD was set (European Commission, 2012b).

Based on *in vitro* human skin studies on the four representative formulations, the dermal absorption values for fosetyl-Al are comprised between 0.1% and 1% for the concentrates and 3% and 6% for the dilutions. Exposure estimates were provided for the representative uses on grape, pome fruit and citrus. For 'FEA + FLC WG 71.11', estimated operator exposure is below the AOEL without the use of personal protective equipment (PPE) (German model) using a tractor-mounted equipment or a hand-held sprayer on grapes. For the worker, bystander and resident, the predicted exposure is below the AOEL. Concerning 'Fosetyl-AL 80% WP' on citrus and grapes, the predicted exposure for operators is below the AOEL without PPE using a tractor-mounted equipment or a hand-held sprayer. For the worker, the predicted exposure exceeds the AOEL (124%) without PPE and considering multi-application for grapes only (EUROPOEM and EFSA calculator). It is noted that no data are available for a refinement considering the wearing of PPE but the exposure would be likely below the AOEL. No exceedance of the AOEL is reported for bystander and resident exposure estimates. Regarding 'FEA WG 80', for the operators, the predicted exposure is below the AOEL without PPE using a tractor-mounted equipment or a hand-held sprayer on pome fruits. The exposure of worker (without PPE), resident and bystander is below the reference values. Finally, for the use on grapes of 'SIP40958', the predicted exposure of operators, is below the AOEL without PPE when using a tractor-mounted equipment or a hand-held sprayer. For workers, residents and bystanders, the exposure estimates are below the reference values. It is noted that, for information purposes, exposure estimates with the EFSA calculator (EFSA, 2014) have been also provided (France, 2018) and no exceedance of the reference values has been reported.

Concerning the metabolites, the toxicological profile of phosphonic acid has been assessed through several studies testing phosphonic acid or its salts (sodium and potassium phosphonates). They have low acute toxicity and show negative results in genotoxic tests (Ames test, inductest in *Escherichia coli* and *in vivo* micronucleus). In a 13-week rat study, a NOAEL of 400 mg/kg bw per day is set based on soft faeces, increase of water consumption and of urinary sodium excretion. A NOAEL of 200 mg/kg bw per day (corresponding to 347.6 mg/kg bw per day of hydrated monosodium phosphonate tested) has been derived from a 27-month rat study based on soft faeces, urine acidification, decreased efficiency ratio between bodyweight and food and changes on organs weight; and no carcinogenic potential has been reported. Since phosphonic acid is a major metabolite in rat (73% in the urine), its toxicity (including developmental and reproductive toxicity (DART)) is considered covered by the studies performed with fosetyl-Al.

The experts agreed that the reference values for aluminium defined by EFSA in the conclusion on aluminium ammonium sulphate (EFSA, 2012a) should be kept, i.e. an ADI and ARfD of 0.14 mg/kg bw (per day) and an AOEL of 0.002 mg/kg bw per day (oral and dermal absorption value of 1%). An

AAOEL was not proposed. A risk assessment related to the exposure to aluminium has been performed for workers and residents even if aluminium is not included in the residue definition. Therefore, EFSA acknowledge that this assessment is more for informative purpose. It is also noted that the calculations are worst case as any data for a refinement are not available assuming also no degradation of aluminium residues in plants (see Section 3). For 'FEA + FLC WG 71.11', the exposure to aluminium exceeds the AOEL for aluminium for workers (without PPE) but is below for residents. Concerning 'Fosetyl-Al 80% WP', for workers, the predicted exposure is higher than the AOEL without PPE for grapes and with gloves for citrus. For residents, the predicted exposure is below the AOEL. Regarding 'FEA WG 80', the exposure of residents is below the AOEL but above AOEL for workers wearing gloves. For 'SIP40958', the predicted exposure of workers is above AOEL without PPE. For residents the exposure estimate is below the AOEL.

It is noted that, for information purposes, exposure estimates with the EFSA calculator (EFSA, 2014) have been also provided (France, 2018) and the same results as with EUROPOEM are reported for workers. An exceedance of the AOEL has been noted for children for 3 out of 4 formulations.

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).

Fosetyl was discussed at the Pesticides Peer Review Experts' Meeting 173.

Metabolism of fosetyl-Al in primary crops was investigated upon foliar application on fruit crops (citrus, apples, tomatoes), on apples and vine leaves and by dipping followed by a spray treatment on pineapples using ^{14}C fosetyl-Al. Most of the radioactive residues remained on the surface of the fruit or leaves and penetration and translocation to the untreated parts of the plants was limited. The major degradation pathway of fosetyl-Al in fruit crops was shown to be the hydrolytic cleavage of the ethyl ester moiety of fosetyl yielding the formation of ethanol and phosphonic acid as the main identified metabolites of the residues in all crops. Ethanol was subsequently metabolised and incorporated into natural constituents of the plants (D-glucose, cellulose, lignin, starch, fatty acids).

It is noted that the fate of the phosphonic acid moiety of the parent molecule was not investigated in the available plant metabolism data. However and from the residue trials compliant with the representative uses on citrus, pome fruit and grapes, the residue levels of phosphonic acid were found to be much higher compared to the magnitude of fosetyl-Al residues. The residue definition for risk assessment was set as the 'sum of fosetyl, phosphonic acid and their salts, expressed as phosphonic acid' since fosetyl-Al degrades significantly into phosphonic acid under freezer storage conditions. For monitoring, fosetyl cannot be considered a suitable residue marker in view of its degradation into phosphonic acid under storage conditions and as can be seen from the residue trials fosetyl-Al occurred at lower residue levels compared to phosphonic acid residues in the crops at harvest. Although phosphonic acid is predominant in plants resulting from the use of fosetyl-Al, this compound may be formed by other pesticides (disodium phosphonates, potassium phosphonates) or from the use of fertilisers. For monitoring, the same residue definition as for risk assessment can therefore be recommended. Due to the elementary nature of fosetyl-Al, it is expected that the metabolic pattern should be similar in all crops. It is highlighted that a minority opinion of which the RMS considered that only phosphonic acid and its salts should be included in the residue definition for monitoring and risk assessment as it would allow considering other pesticides that are sources of phosphonic acid residues with the purpose of a MRL harmonisation.

Residue trials respectively on oranges and mandarins were submitted in support of the representative use on citrus fruit. None of the residue trials on oranges was compliant with the recommended maximum time interval between each application (90 days) and a complete residue data set on oranges compliant with the critical southern Europe (SEU) GAP and supported by acceptable storage stability data is required (data gap for FAIRITF). A minority opinion of which the RMS considered that four additional GAP-compliant trials only should be provided, analysing for the residue levels immediately before the final application in order to investigate whether the time interval between applications impact significantly the terminal residue levels. A complete residue data set on mandarins was provided.

A sufficient number of acceptable residue trials respectively on pome fruit and on grapes and compliant with the representative uses on these crops were submitted (Bayer CropScience). For the

representative use on grapes (FAIRITF), the submitted residue trials are not compliant with the time interval between application and a complete residue data set on grapes compliant with the critical SEU GAP is required (data gap for FAIRITF). RMS expressed its disagreement regarding this data gap. Finally, four additional residue trials compliant respectively with the northern Europe (NEU) and SEU GAP on grapes are required to complete the residue data set (data gap; OXON SAE Fosetyl Task Force). All the residue trials on apples, pears and grapes were supported by acceptable storage stability data when considering the sum of fosetyl-Al and phosphonic acid. In view of the deficiencies identified regarding the storage stability data on orange peel and pulp submitted by the applicant FAIRITF, valid storage stability data on citrus fruit and covering the maximum storage time period of the residues from the trials on oranges and mandarins are requested (data gap for FAIRITF).

Fosetyl-Al and phosphonic acid can be considered as hydrolytically stable under conditions representative of pasteurisation, baking/brewing/boiling and sterilisation. Processing residue trials were submitted to derive transfer factors for processed commodities of citrus, apples and grapes.

The representative uses are on permanent crops and therefore rotational crops metabolism studies are in principle not requested. Fosetyl-Al and its metabolite ethanol exhibited very low persistence in soil whilst phosphonic acid showed moderate to high persistence (see Section 4). The same residue definition as for primary crops is applicable to the rotational crops. The occurrence of phosphonic acid residues in rotational root crops (radishes), leafy crops (lettuces) and cereals (barley) was also investigated following bare soil application of phosphonic acid at 4.9 mg/kg in soil, representing the concentration resulting from the application of 15 kg/ha of fosetyl-Al (1.4 N rate). Quantifiable residues of phosphonic acid were found only in radish root and lettuce at the 30-day plant-back interval (PBI) (0.8 and 0.76 mg eq./kg, respectively). Rotational crops field trials were also conducted on lettuces, carrots and cereals following treatment of lettuces as a target crop with fosetyl at a total dose rate of 2.3 kg a.s./ha and showed residues of fosetyl and phosphonic acid below the LOQ of the method in all crop parts at the 30-day PBI, except in wheat grain (0.21 mg/kg for phosphonic acid). Since these trials were under dosed compared to the critical GAPs that were assessed in the framework of the Article 12 MRL review (EFSA, 2012b), no conclusion can be drawn on the actual residue levels of fosetyl and phosphonic acid in rotational crops. In case of any future use on crops that might be rotated, additional rotational crop field trials should be provided to determine the actual magnitude of fosetyl-Al and phosphonic acid residues. Alternatively, Member States should take the appropriate risk mitigation measures in order to avoid the presence of fosetyl-Al and phosphonic acid residues in rotational crops.

In ruminants, fosetyl-Al was extensively degraded into phosphonic acid and ethanol and was never recovered in milk and tissues. Ethanol was then further excreted as CO_2 or reincorporated into natural products such as carbohydrates, glycogen, saponifiable fatty acids and lipids and amino acids. Residues of fosetyl-Al and ethanol were found in the stomach contents and in urine only. The magnitude of fosetyl-Al and phosphonic acid residues in ruminants was investigated in a feeding study with lactating cows. At the calculated dietary burden residues of fosetyl-Al and phosphonic acid were found to be below the LOQ of the method in milk and other animal commodities. Since phosphonic acid is the predominant compound of the residues in feed items, the residue definition for monitoring and risk assessment for ruminant matrices is set as phosphonic acid only.

A metabolism study on poultry was not triggered considering the representative uses. A fish metabolism study was also not required as citrus, pome fruit and grapes are not feeding stuffs for fish.

Field residue trials analysing for fosetyl-Al and phosphonic acid residues in orange flowers and nectar showed significant residue levels of both compounds (above the LOQ of 0.5 mg/kg for fosetyl and phosphonic acid, respectively). Considering the residue levels in nectar, the RMS proposed to apply a transfer factor of 1 to determine the residues levels and a MRL in honey which is affected by some uncertainties considering that the transformation of nectar to honey may involve concentration and a hydrolysis step. This approach should therefore be considered as indicative only in absence of clear guidance for the determination of residues in honey. Moreover these trials are not supported by storage stability data. Since pome fruit and grapes can also be visited for pollen and nectar collection (EFSA, 2013b) and treatment can take place at flowering, residues of fosetyl-Al and phosphonic acid in pollen and bee products for human consumption resulting from residues taken up by honeybees from pome fruit and grapes at blossom cannot be excluded and further information is requested (data gap, FAIRITF, Bayer CropScience, OXON SAE Fosetyl Task Force).

No chronic intake concern was identified using the MRL proposals for the representative uses (theoretical maximum daily intake (TMDI): 73% of ADI, German child).

Toxicological reference values have been set for aluminium (see Section 2). Although aluminium was not included in the residue definition for risk assessment, an indicative consumer exposure to

aluminium residues potentially present in commodities treated with fosetyl-Al has been conducted based on a worst-case estimation of its residue levels in citrus, grapes and pome fruit assuming also no degradation of aluminium residues in plants along with the preharvest interval (PHI) value. Whilst the chronic intake was found to be acceptable, an acute intake concern cannot be excluded. Data for refinement of aluminium residues in plants are not available except in oranges field trials following dipping or spray treatment where the residue levels of aluminium were below the LOQ (1 mg/kg) in the pulp. EFSA acknowledges that this assessment is more for informative purpose.

The toxicological reference values for fosetyl-Al and phosphonic acid and the residue definitions for both enforcement and risk assessment in plants have been changed compared to those used in the review of the existing MRLs for fosetyl-Al (EFSA, 2012b). Based on the proposed ADI of 1 mg/kg bw per day for phosphonic acid and using the supervised trials median residue (STMR) values, no chronic intake concern was identified for the consumers for all the existing uses assessed under the Article 12 MRL review (international estimated daily intake (IEDI): 29% of the ADI, German child).

4. Environmental fate and behaviour

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, fosetyl-Al exhibited very low persistence, forming the major (> 10% applied radioactivity (AR)) metabolite ethanol (max. 78% AR), which exhibited very low persistence. Phosphonic acid, which exhibited moderate to high persistence, was identified as a significant degradation product of fosetyl-Al, but it was not quantified, and thus, a maximum level of 100% AR was assumed for this metabolite in the exposure assessment. Mineralisation of the ethyl ^{14}C radiolabel to carbon dioxide accounted for max. 19.6% AR after 15 h. The formation of unextractable residues (not extracted by acetonitrile/water) for this radiolabel accounted for max. 47% AR after 16 h. In anaerobic soil incubations, fosetyl-Al was rapidly degraded, with the degradation pathway similar to that under aerobic conditions. Photodegradation of fosetyl-Al on soil was not studied due to rapid degradation in soil in dark conditions. However, the contribution of photolysis to the dissipation of fosetyl-Al from the soil is regarded as negligible. Photodegradation studies showed that phosphonic acid was degraded faster under illuminated conditions. Therefore, an effect of light on phosphonic acid degradation cannot be excluded. Due to negligible light absorption by phosphonic acid above 290 nm, only indirect photolysis could occur. The likely product of soil photolysis of phosphonic acid is phosphate. Fosetyl-Al was not adsorbed on soil, no reliable data were determined due to the fast degradation in soil, and thus the worst case default adsorption endpoints were used in the exposure assessment. Phosphonic acid exhibited medium to slight mobility. It was concluded that the adsorption of phosphonic acid was not pH dependent. For phosphonic acid, adsorption endpoints from the EFSA conclusion on disodium phosphonate (EFSA, 2013a) and adsorption endpoints from the present EFSA conclusion were pulled together to derive endpoints to be used in the exposure assessment. No assessment of the adsorption and leaching potential of the major soil metabolite ethanol was carried out. However, as reported in the previous EFSA conclusion on fosetyl (EFSA, 2006), the potential for ethanol to leach to groundwater is considered to be insignificant and is covered by the modelling carried out for the parent fosetyl-Al. Field DT_{50} estimates were not available for phosphonic acid which, when dosed in laboratory soil incubations, had single first order DT_{50} greater than 60 days. In this situation, field DT_{50} and DT_{90} estimates are needed according to the data requirements and this has been identified as a data gap.

In laboratory incubations in dark aerobic natural sediment water systems, fosetyl-Al exhibited low persistence, forming the major metabolites ethanol (only transient product of biotransformation, max. 19.2% after 2 days) and phosphonic acid (100% AR assumed in water and sediment). The unextractable sediment fraction was the major sink for the ethyl ^{14}C radiolabel, accounting for 19.4–20.8% AR at study end (100 days). Mineralisation of this radiolabel accounted for 70.9–75.9% AR at the end of the study (100 days). The rate of decline of fosetyl-Al in laboratory sterile and natural aqueous photolysis experiments was slow relative to that occurring in the aerobic sediment water incubations.

The rate of decline of fosetyl-Al in indirect photolytic transformation in sterile natural water and direct photolytic transformation in pure water was slow relative to that occurred in the aerobic sediment water incubations. Irradiation of ^{14}C-fosetyl-Al in sterile natural and pure sterile water resulted in the formation of ethyl phosphate (max 24.3% at 7 days), ethanol (max. 14.3% at 7 days) and acetic acid (max 44.6% at 7 days). Overall, photolysis is unlikely to contribute significantly to the degradation of fosetyl-Al from the aquatic environment.

The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for phosphonic acid, using the FOCUS (2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). For the active substance fosetyl-Al, appropriate step 3 and step 4 calculations were available. The step 4 calculations appropriately followed the FOCUS (2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 57–91% spray drift reduction), and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80%, erosion run-off by 95%) being implemented for the run-off scenarios. The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations. However, risk managers and others may wish to note that whilst run-off mitigation is included in the step 4 calculations available, the FOCUS (2007) report acknowledges that for substances with K_{Foc} < 2,000 mL/g (i.e. fosetyl-Al), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature, than for more strongly adsorbed compounds.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (2009) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4 for the active substance fosetyl-Al and metabolite phosphonic acid. To be consistent with the approach already accepted during the assessment of other inorganic substances like disodium phosphonates (EFSA, 2013a), K_f values of phosphonic acid were kept constant in all soil horizons of the corresponding FOCUS scenario except for the formulated product 'Fosetyl-Al 80% WP' where K_f was modified considering different sorption factors in each horizon. The potential for groundwater exposure from the representative uses by fosetyl-Al above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios for fosetyl-Al and phosphonic acid. Ethanol is the main degradation product of fosetyl-Al. Concerning the risk of groundwater contamination, no formal assessment of the adsorption and leaching potential of the major soil metabolite ethanol was carried out. However because of its short soil half-life (in the same range as the parent fosetyl-Al), the potential for ethanol to leach to groundwater is considered by EFSA (2006) to be insignificant and is covered by the modelling carried out for the parent fosetyl-Al.

Information to address the effect of water treatments processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water, were not included in the dossier. This has been identified in Section 7 as a data gap and as an assessment not finalised (see Section 9.1). Article 4 (approval criteria for active substances) 3.(b) of Regulation (EC) No 1107/2009 indicates that information on this is needed for the decision making on EU level approval.

The applicants stated that a search performed for fosetyl-Al and its metabolites in the scientific peer-reviewed open literature and following the EFSA guidance revealed no results regarding monitoring data. However, at least a public French database on groundwater resources gathering should have been considered by the applicants, therefore a data gap was identified in Section 7 for providing monitoring data.

The PEC in soil, surface water, sediment, and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion.

In the previous EFSA conclusion on fosetyl (EFSA, 2006), the potential impact of the additional aluminium added to soil from the use of fosetyl-Al compared to the amounts that occur naturally in soils was assessed, and it was concluded that aluminium resulting from the use of fosetyl-Al is expected to have no significant impact on the environment. This conclusion is still considered valid.

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 (2013b).

Some aspects of the risk assessment of fosetyl-Al were discussed at the Pesticide Peer Review teleconference 167.

The technical specification for one applicant is not covered by the ecotoxicological batches.

It is noted that ethanol was identified as one of the major metabolites of fosetyl-Al in soil; however, due to the transient nature of this metabolite a low risk to soil organisms could be concluded for all the representative uses.

A low acute and long-term risk to **birds** and **mammals** for fosetyl-Al and its pertinent metabolites was concluded for all routes of exposure and for all the representative uses.

A low acute and chronic risk to **aquatic organisms** was concluded for fosetyl-Al for all the representative uses provided that mitigation measures are implemented. It is noted that for the

representative product 'SIP40958', containing cymoxanil and copper in addition to fosetyl-Al, valid acute aquatic toxicity studies data were not available; this may need to be further addressed at Member States level. It is additionally noted that the formulated product 'FEA + FLC WG 71.11' resulted in a higher acute toxicity to fish with respect to the active substance and the formulated products containing only fosetyl-Al. For the metabolite phosphonic acid, a low acute and chronic risk was concluded for the representative uses on grapes (three applications at 2.0 kg/ha; four applications at 2.64 kg a.s./ha) and citrus. For the uses on pome fruits and grapes (four applications at 1.35 kg a.s./ha), a high acute risk was identified at FOCUS step 2 level (data gap). It is noted that the Regulatory acceptable concentration acute (RACac) for phosphonic acid was changed by EFSA during the drafting of the conclusions since the lower available endpoint is the $LD_{50} > 35.7$ mg/L. The RACac proposed by the RMS was 400 mg/L; however, whilst it is recognised that all the available endpoints are unbounded values, it cannot be ensured that the proposed RACac would cover also *Lepomis macrochirus*. The RMS disagreed with this proposal.

Suitable acute (oral and contact) and chronic (adult and larvae) toxicity studies on honey**bees** were available. It is noted that chronic data (larvae and adult) were not available for the two formulations containing more than one active ingredient ('FEA + FLC WG 71.11' and 'SIP40958'); this may need to be further addressed at Member States level. Information on potential sub-lethal effects on honeybees (e.g. effects on hypopharyngeal glands (HPG)) was not available (data gap). A suitable assessment for accumulative effects was not available. In addition to the standard studies, a colony feeding study and five semi-field studies (tunnel tests in line with OECD 75) performed with 'Fosetyl-Al WG 80' were available. It is noted that the design of these studies presents some limitations according to the EFSA Guidance Document on bees (EFSA, 2013b). In the colony feeding study, the egg termination rate was significantly higher in the test item group when compared to the control. In the available semi-field studies adverse effects were not observed; however, these studies cannot be confirmed as being representative of the GAP (i.e different application pattern in term of number of applications and application rate or estimation of the application rate not available). A risk assessment in line with the Guidance Document on Terrestrial Ecotoxicology (European Commission, 2002a) was provided which demonstrated a low acute (contact and oral) risk to honeybees for all the representative uses. It is, however, noted that the presented assessment does not cover the chronic risk to honeybee larvae and adult. Considering the above a data gap was identified by EFSA for a risk assessment in line with the EFSA (2013b) for fosetyl-aluminium and for any metabolites potentially formed in pollen and nectar.

Apart from acute toxicity data on bumblebees, no data were available for non-apis bees.

A low risk to **non-target arthropods** was concluded for all the representative uses.

In the case of **earthworms** and other **soil organisms**, only studies performed with the formulated products were available. This was considered acceptable. For collembola and soil mites, data were not available for the 'Fosetyl-Al 80% WP'. In the latter case, the extrapolation of the toxicity endpoints from 'Fosetyl-Al WG 80' was considered acceptable. By considering these data in the risk assessment, a low risk was concluded for fosetyl-Al for all the representative uses. Studies addressing the toxicity of the metabolite phosphonic acid to earthworms were not available; however, considering the rapid formation of this metabolite in soil, the toxicity of this metabolite was considered to be covered by the available studies with 'Fosetyl-Al 80% WP' and 'Fosetyl-Al WG 80'. A low risk to soil organisms including earthworms was concluded for the metabolite phosphonic acid for all the representative uses.

A low risk to **soil microorganisms** was concluded for fosetyl-Al and phosphonic acid for all the representative uses.

A low risk to **non-target terrestrial plants** was concluded for the use on pome fruits of 'Fosetyl-Al WG 80'. Since for 'FEA+FLC WG 71.11', 'Fosetyl-Al 80% WP' and 'SIP40958' only studies addressing effects on vegetative vigour were available a data gap was identified by EFSA. The RMS disagreed with this proposal.

A low risk to organisms used in **biological methods of sewage treatment** was concluded for all the representative uses.

The available ecotoxicological data are not sufficient to conclude on the endocrine disruption potential of fosetyl-Al. Pending on the outcome of the data gap in Section 2, further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of fosetyl-Al.

6. 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)	Persistence	Ecotoxicology
Fosetyl-Al	Very low persistence single first order DT_{50} 0.01–0.06 days (DT_{90} 0.04–0.2 days; laboratory conditions at 20°C, 40–75% MWHC soil moisture)	Low risk
Phosphonic acid	Moderate to high persistence single first order DT_{50} 28–130 days and biphasic kinetics DT_{50} 31 to > 1,000 days (DT_{90} 91 to > 1,000 days; laboratory conditions at 20°C, 45–75% MWHC soil moisture)	Low risk
Ethanol	Very low persistence single first order DT_{50} 0.09–0.18 days (DT_{90} 0.28–0.58 days; laboratory conditions at 20°C, 40–75% MWHC soil moisture)	Low risk

DT_{50}: period required for 50% dissipation; DT_{90}: period required for 90% dissipation; MWHC: maximum water-holding capacity.

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
Fosetyl-Al	Default conservative assumption K_{Foc} 0.1 mL/g	No	Yes	Yes
Phosphonic acid	Medium to slight mobility K_{Foc} 193–3,038 mL/g	No	Yes but no exposure so assessment not required	No
Ethanol	Covered by the parent compound	No	No exposure, assessment not required	No

K_{FOC}: Freundlich organic carbon adsorption coefficient.
(a): FOCUS scenarios or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Fosetyl-Al	Low risk
Phosphonic acid	Data gap for uses on pome fruits and grapes (4 applications at 1,350 g a.s./ha), low risk for the remaining uses

a.s.: active substance.

Table 4: Air

Compound (name and/or code)	Toxicology
Fosetyl-Al	LC_{50} rat > 5.11 mg/L air per 4 h (nose only)

LC_{50}: lethal concentration, median.

7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- A detailed reporting of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on human health (e.g. input parameters, key words, relevance/reliability used by all the applicants are missing in the RAR) and published within the 10 years before the date of submission of the dossier, to be conducted and reported in the RAR in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011; relevant for all representative uses evaluated; submission date proposed by the applicant: unknown).
- ILV of the Quick Method for the Analysis of numerous Highly Polar Pesticides in Foods of Plant Origin via LC–MS/MS involving Simultaneous Extraction with Methanol (QuPPe-Method) Version 9.3 (relevant for the representative uses evaluated with 'Fosetyl-Aluminium 80 WG' formulation, submission date proposed by the applicant: unknown; see Section 1).
- Analytical method for the determination of phosphonic acid in soil with a LOQ of 0.05 mg/kg. (relevant for the representative uses evaluated with 'SIP40958' formulation; submission date proposed by the applicant: unknown; see Section 1).
- Analytical method for the determination of phosphonic acid in drinking water with an LOQ of 0.1 μg/L and its ILV (relevant for the representative uses evaluated with 'SIP40958' formulation; submission date proposed by the applicant: unknown; see Section 1).
- Additional validation data of the ILV method for the determination of residues of phosphonic acid in drinking water (relevant for the representative uses evaluated with 'Fosetyl-Aluminium 80 WG' formulation; submission date proposed by the applicant: unknown; see Section 1).
- The (eco)toxicity profile of 2 impurities is missing (relevant for Bayer CropScience representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5).
- The published DNT study on aluminium (Poirier et al., 2011) should be provided. Pending on the analysis of this study, a DNT for fosetyl-Al might be requested (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- The involvement of the parathyroid hormones in the hypothesised mode of action of fosetyl-Al should be clarified. Pending this data gap, further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of fosetyl-Al in non-target organisms (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5).
- A proposal for level 2/3 assessment according to the OECD conceptual framework is needed to conclude on the endocrine disruptor potential of fosetyl-Al. Pending this data gap, further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of fosetyl-Al in non-target organisms (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5).
- Valid storage stability data on citrus fruit and covering the maximum storage time period of the residues from the trials on oranges and mandarins are requested (relevant for the representative uses evaluated in citrus; submission date proposed by the applicant FAIRITF: unknown; see Section 3).
- A complete residue data set on oranges and compliant with the critical SEU GAP (relevant for the representative uses evaluated in citrus; submission date proposed by the applicant FAIRITF: unknown; see Section 3).
- A complete residue data set on grapes compliant with the critical SEU GAP (relevant for the representative use evaluated in grapes; submission date proposed by the applicant FAIRITF: unknown; see Section 3).
- Four additional residue trials on grapes compliant respectively with the NEU and SEU GAP (relevant for the representative use evaluated in grapes; submission date proposed by the applicant OXON: unknown; see Section 3).

- Determination of residues of fosetyl-Al and phosphonic acid in pollen and bee products for human consumption resulting from residues taken up by honeybees from pome fruit and grapes at blossom (relevant for the representative uses on pome fruit and grapes; submission date proposed by the applicants FAIRITF, Bayer CropScience, OXON SAE Fosetyl Task Force: unknown; see Section 3).
- Reliable field DT_{50} and DT_{90} estimates from three different field trial sites were not available for phosphonic acid. These are needed according to the results of laboratory incubations and the data requirements (relevant for all representative uses, submission date proposed by the applicant: unknown; see Section 4).
- The effect of water treatment processes on the nature of residues present in surface, when surface water is abstracted for drinking water (Article 4 (approval criteria for active substances) 3. (b) of Regulation (EC) No 1107/2009) has not been assessed. In the first instance, a consideration of the processes of ozonation and chlorination may be considered appropriate. If an argumentation is made that concentrations at the point of extraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be in groundwater and surface water, as well as the active substance (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Available monitoring data (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Further information to address the risk to aquatic organisms for phosphonic acid (relevant for the uses on pome fruits and grapes (4 applications at 1,350 g a.s./ha); submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to honeybees for fosetyl-Al and its metabolites formed in pollen and nectar (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information on potential sub-lethal effects on honeybees (e.g. effects on HPG) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the effects on non-target terrestrial plants for 'FEA+FLC WG 71.11', 'Fosetyl-Al 80% WP' and 'SIP40958' (seedling emergence) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

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

- Measures to mitigate the risk to aquatic organisms are needed for the uses on pome fruits and for all uses on grapes (see Section 5).

9. Concerns

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 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[5] 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.

1) The consumer risk assessment cannot be finalised considering the identified data gaps for sufficient residue trials compliant with the representative uses on citrus and grapes. (see Section 3).

[5] 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, p. 127–175.

2) The consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of surface water and groundwater that might contain fosetyl-Al and its metabolites (see Section 4).

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 the 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.

None identified for the representative uses assessed.

9.3. Overview of the concerns identified for each representative use considered

(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 5.)

The technical material specification proposed by Bayer could not be compared to the material used in the (eco)toxicity testing and that was used to derive the toxicological reference values.

Table 5: Overview of concerns

Representative use		**Grapes (3 × 2.0 kg/ha)**	**Grapes (4 × 1.35 kg/ha)**	**Citrus**	**Grapes (4 × 2.64 kg/ha)**	**Pome fruits**
Operator risk	Risk identified					
	Assessment not finalised					
Worker risk	Risk identified	X (Al)**	X (Al)**	X (Al)**	X (fosetyl-Al* and Al**)	X (Al)**
	Assessment not finalised					
Resident/ bystander risk	Risk identified					
	Assessment not finalised					
Consumer risk	Risk identified	X (Al)**	X (Al)**	X (Al)**	X (Al)**	X (Al)**
	Assessment not finalised	X^{2}	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	X^{2}
Risk to wild non-target terrestrial vertebrates	Risk identified					
	Assessment not finalised					

Representative use		Grapes (3 × 2.0 kg/ha)	Grapes (4 × 1.35 kg/ha)	Citrus	Grapes (4 × 2.64 kg/ha)	Pome fruits
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified					
	Assessment not finalised					
Risk to aquatic organisms	Risk identified		X			X
	Assessment not finalised					
Groundwater exposure to active substance	Legal parametric value breached					
	Assessment not finalised					
Groundwater exposure to metabolites	Legal parametric value breached					
	Parametric value of 10 µg/L[(a)] breached					
	Assessment not finalised					

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.

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

*: It is noted that no data are available for a refinement considering the wearing of PPE but the exposure would be likely below the AOEL.

**: A risk assessment related to the exposure to aluminium has been characterised for workers, residents and consumers, although aluminium is not included in the residue definition. Exceedance of the reference values have been identified for workers and consumers (acute). EFSA acknowledge that this assessment is more for informative purpose. It is also noted that the calculations are worst case as data for refinement are not available assuming also no degradation of aluminium residues in plants.

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Abbreviations

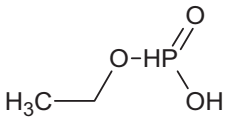
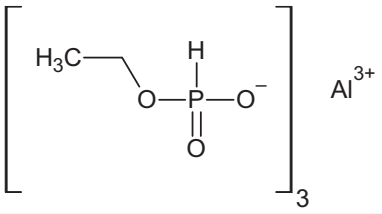
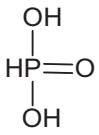
a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
DAR	draft assessment report
DART	developmental and reproductive toxicity
DNT	developmental neurotoxicity
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
EEC	European Economic Community
EUROPOEM	European Predictive Operator Exposure Model
f(twa)	Time-weighted average factor
FAO	Food and Agriculture Organization of the United Nations
FEA	fosetyl-aluminium
FID	flame ionisation detector
FLC	fluopicolide
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GC	gas chromatography
HPG	hypopharyngeal glands
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ILV	Independent Laboratory Validation
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
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_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MRL	maximum residue level
MWHC	maximum water-holding capacity
NEU	northern Europe
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PBI	plant-back interval
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
PHI	preharvest interval
PPE	personal protective equipment
RAR	Renewal Assessment Report
RACac	Regulatory acceptable concentration acute
RMS	rapporteur Member State
SEU	southern Europe
SMILES	simplified molecular-input line-entry system
STMR	supervised trials median residue
TMDI	theoretical maximum daily intake
UF	uncertainty factor
WG	water-dispersible granule
WP	wettable powder
WHO	World Health Organization

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

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5307

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
Fosetyl	ethyl hydrogen phosphonate O=P(O)OCC VUERQRKTYBIULR-UHFFFAOYSA-N	
Fosetyl-aluminium	aluminium tris(ethyl phosphonate) [Al+3].[O-]P(=O)OCC.[O-]P(=O)OCC.[O-]P(=O)OCC ZKZMJOFIHHZSRW-UHFFFAOYSA-K	
Phosphonic acid	phosphonic acid O=P(O)O ABLZXFCXXLZCGV-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 December 2014).
(c): ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 December 2014).