CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance azadirachtin (Margosa extract)

European Food Safety Authority (EFSA),
Maria Arena, Domenica Auteri, Stefania Barmaz, Alba Brancato, Daniela Brocca, Laszlo Bura, Luis Carrasco Cabrera, Arianna Chiusolo, Daniele Court Marques, Federica Crivellente, Chloe De Lentdecker, Mark Egsmose, Gabriella Fait, Lucien Ferreira, Marina Goumenou, Luna Greco, Alessio Ippolito, Frederique Istace, Samira Jarrah, Dimitra Kardassi, Renata Leuschner, Christopher Lythgo, Jose Oriol Magrans, Paula Medina, Ileana Miron, Tunde Molnar, Laura Padovani, Juan Manuel Parra Morte, Ragnor Pedersen, Hermine Reich, Angela Sacchi, Miguel Santos, Rositsa Serafimova, Rachel Sharp, Alois Stanek, Franz Streissl, Juergen Sturma, Csaba Szentes, Jose Tarazona, Andrea Terron, Anne Theobald, Benedicte Vagenende and Laura Villamar-Bouza

Abstract

The conclusions of the EFSA following the peer review of the initial risk assessments carried out by the competent authority of the rapporteur Member State, Germany, for the pesticide active substance azadirachtin are reported. The context of the peer review was that required by Regulation (EC) No 1107/2009 of the European Parliament and of the Council. The conclusions were reached on the basis of the evaluation of the additional representative use of azadirachtin as an acaricide on greenhouse ornamentals. Conclusions are also represented for the representative use evaluated for the approval of azadirachtin, which was as an insecticide on potatoes. 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 identified.

Keywords: azadirachtin, peer review, risk assessment, pesticide, acaricide, insecticide

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Correspondence: pesticides.peerreview@efsa.europa.eu

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Summary

Regulation (EC) No 1107/2009 (hereinafter referred to as 'the Regulation') lays down, *inter alia*, the detailed rules as regards the procedure for the assessment of applications for amendment to the conditions of approval of active substances.

Azadirachtin was approved on 1 June 2011 by Commission Implementing Directive 2011/44/EU, following a peer review of the risk assessment as set out in the European Food Safety Authority (EFSA) Conclusion on azadirachtin, issued on 11 October 2010. It was a specific provision of the approval that only uses as insecticide may be authorised. In accordance with Article 7 of the Regulation, the rapporteur Member State (RMS), Germany, received an application from Trifolio-M GmbH, on 27 February 2012 for amendment to the conditions of approval of the active substance azadirachtin to allow other uses as an acaricide to be authorised.

The RMS provided its initial evaluation of the dossier in the form of an Addendum to the Draft Assessment Report (DAR) and Additional Report, which was received by EFSA on 10 January 2013. The peer review was initiated on 25 January 2013 by dispatching the Addendum for consultation of the Member States and the applicant Trifolio-M GmbH, EFSA also provided comments.

Following consideration of the comments received on the Addendum, it was concluded that additional information should be requested from the applicant and that there was no need to conduct an expert consultation, and that EFSA should adopt a conclusion on whether azadirachtin can be expected to meet the approval criteria provided for in Article 4 of the Regulation, also taking into consideration recital (10) of the Regulation.

The conclusions of the first inclusion were reached on the basis of the evaluation of the representative use of azadirachtin as an insecticide on potatoes, as proposed by the applicant. The conclusions laid down in this report were reached on the basis of additionally evaluating the representative use of azadirachtin as an acaricide on greenhouse ornamentals, as proposed by the applicant for amendment of the conditions of approval. Full details of the representative uses can be found in Appendix A of this report. Conclusions relating to the representative uses on potatoes considered in the EFSA conclusion finalised on 11 October 2010 have been maintained in this document.

Furthermore, it was a specific provision of the approval by Commission Implementing Directive 2011/44/EU that the applicant was required to submit to the European Commission further studies on *the relationship between azadirachtin A and the rest of the active components in the neem seeds extract with respect to amount, biological activity and persistence, in order to confirm the lead active compound approach with regard to azadirachtin A and to confirm specification of the technical material, residue definition and groundwater risk assessment* by 31 December 2013.

In accordance with the specific provision, the applicants, Trifolio-M GmbH, Sipcam S.p.A and Mitsui AgriScience International S.A./N.V, submitted an updated dossier in December 2013, which was evaluated by the designated RMS, Germany, in the form of Addenda to the Additional Report. In compliance with guidance document SANCO 5634/2009-rev.6.1, the RMS distributed the Addenda to Member States, the applicants and EFSA for comments on 10 October 2017. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 15 January 2018. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table that is considered as background document to this conclusion. This conclusion is, therefore, covering both assessments.

A data gap was identified for all sections as regards a search of the scientific peer-reviewed open literature relevant to the scope of the application for amendment to the conditions of approval.

In the section identity physical and chemical properties and analytical methods, no data gaps were identified. The confirmatory data supported that azadirachtin A can be considered as a lead substance from the point of view of application and efficacy.

The confirmatory data requirement to investigate the relationship between azadirachtin A and the rest of the active components in the neem seeds extracts [...] in order to confirm the lead active compound approach with regard to azadirachtin has not been addressed from a toxicological point of view since the relative toxicity of the different components of the extracts is unknown and the previously set data gap remains. The toxicological reference values are based on the full extracts; it is noted that they should be reconsidered in view of the new information given during this procedure, but no concern is identified at this stage with regard to the values currently in place. A data gap set during the previous azadirachtin peer review has been fulfilled, and it has been shown that the extracts from the three sources are unlikely to be genotoxic and the toxicological reference values are applicable to the three sources – as full extracts. Non-dietary exposure assessment to the new

proposed use in ornamentals did not identify a concern for operators, workers, bystanders and residents, provided that the ornamentals are grown in permanent greenhouses.

Even though a steady degradation of 11 limonoids present in azadirachtin extracts was demonstrated in one decline trial in lettuce, which is still to be validated (data gap), information is not available on the breakdown products of these compounds. Moreover, the fate of non-limonoidic components in the azadirachtin extracts is unknown. It is still not clear whether the lead component approach using azadirachtin A is appropriate for the consumer dietary risk assessment in general, and further clarification should be attempted. As for the representative use in potatoes, an indicative consumer risk assessment was conducted using several assumptions and highlighting the uncertainties caused by the existing information gaps. The use on ornamentals was not assessed in the residues section as not deemed relevant for consumer dietary exposure and risk assessment, provided ornamentals are not rotates with crops for human consumption.

With respect to fate and behaviour in the environment, the confirmatory data request with respect to the groundwater assessment cannot be considered completed or satisfied with the available information provided. Further data would also be needed to clarify the residue definitions for risk assessment and monitoring of the different environmental compartments. Previously identified data gaps have been confirmed or redefined in accordance with the information provided. A data gap is identified for the applicant to complete the aquatic risk assessment for all European Union (EU) scenarios relevant for the proposed use as acaricide for ornamentals in greenhouse.

For the representative use to potatoes, the risk to non-target organisms from azadirachtin A was assessed as low provided that risk mitigation measures are used to protect aquatic organisms and non-target arthropods. However, it is not clear whether the lead component approach using azadirachtin is appropriate for the risk assessment for aquatic organisms, soil organisms and non-target arthropods, and therefore, a data gap was identified. The risk to aquatic organisms from the additional use to ornamentals could not be finalised as the surface water exposure assessment is open. The risk to all other non-target organisms is low provided that the ornamentals are grown in permanent greenhouses.

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Background

Regulation (EC) No 1107/2009[1] (hereinafter referred to as 'the Regulation') lays down, *inter alia*, the detailed rules as regards the procedure for the assessment of applications for amendment to the conditions of approval of active substances. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States (MSs) and the applicant(s) for comments on the initial evaluation in the Draft Assessment Report (DAR) provided by the rapporteur Member State (RMS) and the organisation of an expert consultation where appropriate.

In accordance with Article 12 of the Regulation, EFSA is required to adopt a conclusion on whether an active substance can be expected to meet the approval criteria provided for in Article 4 of the Regulation (also taking into consideration recital (10) of the Regulation) within 120 days from the end of the period provided for the submission of written comments, subject to an extension of 30 days where an expert consultation is necessary, and a further extension of up to 150 days where additional information is required to be submitted by the applicant in accordance with Article 12(3).

Azadirachtin was approved on 1 June 2011 by Commission Implementing Directive 2011/44/EU[2], following a peer review of the risk assessment as set out in the EFSA Conclusion (EFSA, 2011b) on azadirachtin, issued on 11 October 2010. It was a specific provision of the approval that only uses as insecticide may be authorised. In accordance with Article 7 of the Regulation, the RMS, Germany, received an application from Trifolio-M GmbH, on 27 February 2012 for amendment to the conditions of approval of the active substance azadirachtin to allow other uses as an acaricide to be authorised.

The RMS provided its initial evaluation of the dossier in the form of an Addendum to the DAR and Additional Report (Germany, 2013), which was received by EFSA on 10 January 2013. The peer review was initiated on 25 January 2013 by dispatching the Addendum to the MSs and the applicant, Trifolio-M GmbH, for consultation and comments. EFSA also provided comments. In addition, the EFSA conducted a public consultation on the Addendum. The comments received were collated by the EFSA and forwarded to the RMS for compilation and evaluation in the format of a Reporting Table. The applicant was invited to respond to the comments in column 3 of the Reporting Table. The comments and the applicant's 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 applicant in accordance with Article 12(3) of the Regulation were considered in a telephone conference between the EFSA, the RMS and the European Commission on 30 May 2013. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation, thereof it was concluded, that additional information should be requested from the applicant and that there was no need to conduct an expert consultation, and that EFSA should adopt a conclusion on whether azadirachtin can be expected to meet the approval criteria provided for in Article 4 of the Regulation, also taking into consideration recital (10) of the Regulation.

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 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 were reported in the final column of the Evaluation Table.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of azadirachtin as an insecticide on potatoes and as an acaricide in ornamentals, as proposed by the applicant. Full details of the representative uses can be found in Appendix A to this report. The conclusions of the first inclusion were reached on the basis of the evaluation of the representative use of azadirachtin as an insecticide on potatoes, as proposed by the applicant. The conclusions laid down in this report were reached on the basis of additionally evaluating the representative use of azadirachtin as an acaricide on greenhouse ornamentals, as proposed by the applicant for amendment of the conditions of approval. Full details of the representative uses can be found in Appendix A of this report. Conclusions relating to the representative uses on potatoes considered in the EFSA conclusion finalised on 11 October 2010 have been maintained in this document.

[1] 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 No L 309, 24.11.2009, p. 1–50.

[2] Commission Implementing Directive 2011/44/EU of 13 April 2011 amending Council Directive 91/414/EEC to include azadirachtin as active substance and amending Commission Decision 2008/941/EC. OJ L 100, 14.4.2011, p. 43–46.

Furthermore, it was a specific provision of the approval by Commission Implementing Directive 2011/44/EU that the applicant was required to submit to the European Commission further studies on *the relationship between azadirachtin A and the rest of the active components in the neem seeds extract with respect to amount, biological activity and persistence, in order to confirm the lead active compound approach with regard to azadirachtin A and to confirm specification of the technical material, residue definition and groundwater risk assessment* by 31 December 2013.

In accordance with the specific provision, the applicants, Trifolio-M GmbH, Sipcam S.p.A and Mitsui AgriScience International S.A./N.V, submitted an updated dossier in December 2013, which was evaluated by the designated RMS, Germany, in the form of Addenda to the Additional Report (Germany, 2017b). In compliance with guidance document SANCO 5634/2009-rev.6.1, the RMS distributed the Addenda to MSs, the applicants and EFSA for comments on 10 October 2017. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 15 January 2018. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table that is considered as background document to this conclusion. This conclusion is, therefore, covering both assessments.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with MSs via a written procedure in February–March 2018.

A list of the relevant endpoints for the active substance as well as the formulation is provided in Appendix A. In addition, a key supporting document to this conclusion is the Peer Review Report, 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, as well as the Reporting Table collecting the comments submitted on the confirmatory data assessment. The Peer Review Report (EFSA, 2018) 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 Addenda to the DAR and Additional Report (amendment of approval conditions),
- the Reporting Table on amendment approval conditions (30 May 2013),
- the Evaluation Table on amendment approval conditions (6 March 2018),
- the comments received on the assessment of the additional information on amendment approval conditions,
- the Reporting Table on confirmatory data assessment (6 March 2018),
- the comments received on the draft EFSA conclusion.

Given the importance of the Addenda to the DAR and the Additional Report including its revisions (Germany, 2017a, 2018) and the Peer Review Report, both documents are considered, respectively, as background documents this conclusion. The documents of the DAR (Germany, 2007, 2009), the final addendum (Germany, 2010) and the Peer Review Report (EFSA, 2010) developed and prepared during the course of the previous review process are made publicly available as part of the background documentation to the original Conclusion issued on 11 October 2010 (EFSA, 2011b).

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 applicant has not demonstrated to have regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Azadirachtin is a common name for an extract from seed kernels of the tropical neem tree *Azadirachta indica*. Azadirachtin A was proposed as the lead substance. There is no ISO common name for this extract. Azadirachtin A is a common name for dimethyl (2a*R*,3*S*,4*S*,4a*R*,5*S*,7a*S*,8*S*,10*R*,10a*S*,10b*R*)-10-acetoxy-3,5-dihydroxy-4-[(1a*R*,2*S*,3a*S*,6a*S*,7*S*,7a*S*)-6a-hydroxy-7a-methyl-3a,6a,7,7a-tetrahydro-2,7-methanofuro[2,3-*b*]oxireno[*e*]oxepin-1a(2*H*)-yl]-4-methyl-8-{[(2*E*)-2-methylbut-2-enoyl]oxy}octahydro-1*H*-naphtho[1,8*a*-*c*:4,5-*b*′*c*′]difuran-5,10a(8*H*)-dicarboxylate (IUPAC).

The representative formulated products for the evaluation were 'NeemAzal-T/S' and 'Oikos' both emulsifiable concentrates (EC) containing 10 g/L and 26 g/L of azadirachtin A, respectively. A FAO specification exists for the EC formulations based on the technical concentrate (TK) from Trifolio-M and EID Parry. (627/EC, May 2006).

The representative uses evaluated comprise applications by spraying to control Colorado beetle on potato in Northern Europe (original representative use for first approval) and to control spider mites on ornamentals in greenhouse (representative use evaluated for the amendment of the conditions of

approval). Full details of the good agricultural practices (GAPs) can be found in the list of endpoints in Appendix A. It should be emphasised, however, that the application rate is expressed on the basis of azadirachtin A content only.

A literature search on the biological activity of possible azadirachtin components in comparison to azadirachtin A was presented. Several of these articles investigated the structure dependence of the effects found by comparing bioassays with azadirachtin A with those of other naturally occurring limonoids or chemical modifications of simpler structures. Data were submitted to conclude that the representative uses of azadirachtin proposed at EU level result in a sufficient insecticidal and acaricidal efficacy against the target organisms.

A data gap has been identified for a search of the scientific peer-reviewed open literature relevant to the scope of the application for amendment to the conditions of approval, dealing with side effects on health, the environment and non-target species and published within the last 10 years before the date of submission of dossier, to be conducted and reported in accordance with the Guidance of EFSA on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011a).

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).

Besides azadirachtin A, azadirachtin contains other compounds that also have biological activity. It should be mentioned that information about the relationship between azadirachtin A and the rest of the active components in the neem seed extract with respect to amount were presented as confirmatory data, presenting the normalised amounts of extracts components of azadirachtin based on an application rate of 25 g azadirachtin A/ha.

It should be emphasised that the manufacturing process has a strong influence on the composition of the TK, and it is necessary to link the specification of the TKs to their respective manufacturing processes. As the three TKs are not chemically equivalent, and there is a significant difference in the azadirachtin A content of the Trifolio-M source compared to the Mitsui and Sipcam sources, it is proposed to consider the active substance as the sum of all biologically active identified compounds in the specification. It is supported, however, that azadirachtin A can be considered as a lead substance from the point of view of application and efficacy. It is proposed to set new specifications for the azadirachtin extracts including all components found at > 10 g/kg during the renewal of approval and to consider the variability of the contents of components; the specifications should also be based on QC data from several years. The proposed azadirachtin A content of the TKs after the first peer review were 250–500 g/kg (Trifolio-M), 120–180 g/kg (Mitsui) and 111–180 g/kg (Sipcam). It should be noted, however, that the batches submitted for the confirmatory data requirement for Mitsui did not meet the proposed specification for the lead substance. The content of the other components of the technical azadirachtin batches presented as confirmatory data for Mitsui and Sipcam did not meet the specifications set in Addendum 1 (Germany, 2010) during the first approval (EFSA, 2011b; European Commission, 2011). The azadirachtin A content in the FAO specification 627/TK (May 2006), applicable to materials from Trifolio-M and EID Parry, is above 250 g/kg up to 500 g/kg and the content of aflatoxins (sum of aflatoxins B_1, B_2, G_1 and G_2) is maximum 0.00003% (300 μg/kg) of the azadirachtin A content. All three TKs meet the requirements of the aflatoxins content of the FAO specification.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity and technical properties of azadirachtin or the respective formulations. The main data regarding the identity of azadirachtin A and its physical and chemical properties are given in Appendix A.

Analytical methods are available for the determination of azadirachtin A and the relevant impurities in the TKs and in the representative formulations. It should be noted that CIPAC methods also exist for the determination of azadirachtin A in the TK and EC formulations. Analytical methods are available for the determination of residues of azadirachtin A in food of plant origin and in the environmental matrices. No methods are available for food of animal origin. As the residue definitions are not

concluded on in any of the environmental compartments, pending on the final residue definitions, data gaps might be identified for enforcement analytical methods. Analytical methods for residues in body fluids and tissues are not required since the neem extract is not classified as toxic or very toxic.

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/222/2000 rev. 7 (European Commission, 2004), SANCO/10597/2003 – rev. 10.1 (European Commission, 2012) and Guidance on Dermal Absorption (EFSA PPR Panel, 2012).

Azadirachtin was discussed at the PRAPeR Experts' Meeting on mammalian toxicology (PRAPeR 79). The batches used in the toxicological studies performed with the Trifolio-M source are within the range of the technical specification proposed for this extract (Neem Azal); however, it is noted that some uncertainty remains as to whether the whole range of the specification would be covered. Insufficient information is available to conclude on the technical specification for the Mitsui (ATI 720) source, and the data gap identified in the previous EFSA conclusion (EFSA, 2011b) remains for information on the composition of the batches used in the toxicological studies conducted with this source. Based on additional genotoxicity data provided on the Mitsui source, showing that this source, as the other two, is unlikely to be genotoxic, the three sources, Trifolio-M, Sipcam and Mitsui, are concluded to be toxicologically equivalent. Considering the quantitative difference in composition of the three extracts, the equivalence is based on the whole extracts and cannot be established based on the azadirachtin A compound. The confirmatory data did not provide information that could change this conclusion since the relative toxicity profile of the different components of the extracts has not been addressed. Regarding the specification, no further information has been provided and the previously set data gap remains for the assessment of the toxicological relevance of the impurities and by-products present in the technical material, with the exception of aflatoxins, which are known relevant impurities.

There is no information on bioavailability as no study could be performed on toxicokinetics and metabolism with azadirachtin. The three sources of azadirachtin extract present low acute toxicity when administered either by the oral, dermal or inhalation routes, they are not skin or eye irritants, but a potential for skin sensitisation is observed with the three sources. Upon short-term exposure, the liver is the main target organ, the relevant no observed adverse effect level (NOAEL) is 32 mg/kg body weight (bw) per day; the three sources presented similar NOAEL values. The two long-term studies submitted are not adequate to conclude on the long-term toxicity or carcinogenicity. The three extracts were clastogenic *in vitro* in chromosomal aberration tests in cultured human lymphocytes. *In vivo* studies with the three extracts did not confirm these positive results and no potential for genotoxicity *in vivo* is attributed to azadirachtin extracts. Fertility and reproductive performance were not impaired by azadirachtin in a valid multigeneration study in rat; reproductive effects observed in humans in the open literature are not relevant to this dossier as the raw material and extraction type are not comparable between the different extracts (the open literature reports on oily extracts or different parts of neem tree other than neem seed kernel). No developmental effects were observed in rats with the Trifolio-M and Sipcam sources; while in rabbits, developmental toxicity was associated with maternal toxicity in a study provided with the Mitsui source. The majority of the experts considered that classification regarding developmental toxicity may not be appropriate. No neurotoxic potential is attributed to azadirachtin.

The previously agreed toxicological reference values were set on the basis that the rabbit developmental toxicity study conducted with the Mitsui source could not be included in the overall toxicological assessment, since at the time of drafting the first conclusion (EFSA, 2011b), the equivalence of the three sources had not been established. The reference values were not reconsidered in the light of this new information from the Mitsui source, they were merely agreed to apply to the three sources. EFSA, therefore, notes that they should be reconsidered when a full review of the assessment is conducted. Currently, the acceptable daily intake (ADI) of azadirachtin extracts remains at 0.1 mg/kg bw per day, based on the 90-day study in rat, applying a safety factor of 300 – an additional safety factor of 3 due to the missing toxicological information on long-term, carcinogenicity and rabbit developmental study. The acceptable operator exposure level (AOEL) remains at 0.1 mg/kg bw per day based on the 90-day rat study, applying the same safety factor of 300 considering the missing information on the bioavailability and rabbit developmental study. The acute reference dose (ARfD) is still 0.75 mg/kg bw based on the developmental study in rat with a maternal NOAEL of 225 mg/kg bw per day, and applying a safety factor of 300 assuming that the rabbit developmental toxicity study is missing. The reference

values are expressed in terms of whole extract and not in terms of the azadirachtin A compound, and they apply to the three extracts from Trifolio-M, Sipcam and Mitsui sources.

The exposure risk assessment is based on the assumption that the 'Neem Azal T/S' formulation is to be applied at amounts of 2.5 L/ha corresponding to amounts of 25 g Azadirachtin A/ha, which would correspond to about 75 g/ha Neem Azal technical (Trifolio-M source). The 'Oikos' formulation is to be applied at amounts corresponding to 25 g azadirachtin A/ha (1 L/ha) corresponding to about 250 g/ha Fortune Aza technical (Sipcam source). However, these values do not cover the whole range of concentrations stated in the technical specifications, and therefore, this approach introduces further uncertainty. According to these assumptions, the estimated operator exposure is below the AOEL when no personal protective equipment (PPE) is worn for both the 'Neem Azal T/S' and 'Oikos' formulations according to the German model for field crop, tractor-mounted applications and according to the UK POEM for home garden sprayers. Worker exposure was estimated to remain below the AOEL for both formulations without the use of PPE. Bystander exposure was estimated to remain below 1% of the AOEL.

Regarding the new proposed use on ornamentals in greenhouses with 'Neem Azal T/S', the maximum application rate is four applications of 90 g NeemAzal T/S extract/ha or 3 L extract/ha. The estimated operator and worker exposure do not exceed the AOEL, even when no PPE is worn, i.e. workers wearing permeable long-sleeved shirt and long trousers, but no gloves. No exposure risk assessment has been provided for bystanders and residents assuming that the greenhouse is a permanent structure preventing emissions of PPPs into the environment after applications (EFSA, 2014).

3. Residues

The assessment in the residue section below is based on the guidance documents listed in the document 1607/VI/97 rev.2 (European Commission, 1999), and the JMPR recommendations on livestock burden calculations stated in the 2004 and 2007 JMPR reports (JMPR, 2004, 2007).

The issue of plant metabolism data was raised in the commenting period by both EFSA and a MS during the first peer review (EFSA, 2011b). An expert discussion was held in PRAPeR TC 33, where it was agreed that the nature of the residue in plants had not been elucidated. It was agreed that, without further data, no conclusion could be drawn. On this basis, a valid risk assessment could not be conducted and a critical area of concern was identified. Subject to the data gap for elucidation of the relevant residue in plants, all of the other data in the residues area should be reassessed (EFSA, 2011b).

To address the request for investigation of the nature of residues, the applicant submitted as part of the confirmatory data a non-radiolabelled residue trial performed in lettuce, analysing 11 components (azadirachtin A, azadirachtin B, [redacted]). To validate this trial, the demonstration of integrity of residues during the entire period of sample storage is still required (data gap).

Provided storage stability of all analytes is demonstrated, the trial in lettuce indicated that levels of all tested components decline following first-order kinetics with similar degradation rates. Residues of azadirachtin A and of azadirachtin B occurred throughout the study in constant proportions of total residues of the known limonoids. However, the database is weak given that only a single trial in lettuce was conducted and that values for most of the compounds tested in addition to azadirachtin A and azadirachtin B were below the limit of quantification (LOQ) at later preharvest intervals (PHIs). Decline trials in apple and tomato with azadirachtin A and azadirachtin B assessed previously (Germany, 2007) did not contradict the findings on the degradation kinetics.

Even though a steady degradation of all the applied 11 limonoids was demonstrated in the lettuce trial, information is still not available on the metabolism or breakdown products of these compounds, i.e. whether their polycycles remain intact and only the functional groups are altered. Data investigating whether or not the polycyclic structure is broken down under environmental conditions and information on photolysis, as required in Section 4, may be used to obtain further clarification on the possible fate of degrading limonoids. Moreover, the fate of non-limonoid (unidentified) components in the different azadirachtin extracts is unknown, which account for a substantial proportion (approximately 50–60%) in the extracts that will be applied to crops.

Based on the currently available information from the lettuce decline trial, azadirachtin A appears a suitable marker to characterise residue levels of azadirachtin (full extracts) shortly after application. The residue definition for monitoring is proposed as azadirachtin A. Since the toxicological reference

values are set for the full extracts (all being of comparable toxicity despite the different proportions of components in these extracts), the residue definition for risk assessment is provisionally proposed as azadirachtin, and specific conversion factors (CF) for each extract were derived. The RMS suggested using the most conservative CF as default factor in order to convert for risk assessment purposes the residues of azadirachtin A from field trials and monitoring, as this approach is assumed to outweigh the uncertainties regarding the unknown metabolism/degradation products of the components in the extracts. It is, however, noted that due to the fast decline of azadirachtin A (less than 5% of the azadirachtin A levels present directly after application were recovered at a PHI of 13 days) and the formation of unknown degradation products of potential relevance, it is still not sufficiently clear whether the lead component approach using azadirachtin A for the consumer dietary risk assessment is appropriate.

As for the representative use in potatoes, one overdosed residue trial investigated potential transport of azadirachtin A from the leaves to tubers, which was not observed (< LOQ). Only three independent field trials in potato are available, all analysing only for azadirachtin A. The assessment in potatoes is based on the assumption that all compounds other than azadirachtin A as well as unknown foliar degradation products show similar translocation and residue behaviour in the potato plant as azadirachtin A. Azadirachtin H*, a major soil metabolite resulting from desacetylation of azadirachtin A (see Section 4), could also be of relevance to the residue situation in potato tubers. Earlier study summaries (Germany, 2007) reported uptake from soil by the roots (azadirachtin A; radiolabelled dihydro azadirachtin A) as well as xylem and phloem translocation to occur in plants.

In that context, and given that residues of azadirachtin A to be used for conversion to the residues relevant for risk assessment were below the LOQ in the potato residue trials, any estimates provided on residues in potato using the proposed CF must be considered as very uncertain.

However, applying the hypothetical assumptions that all components in the azadirachtin extracts as well as their so far unknown metabolites/degradation products have a comparable residue behaviour (e.g. degradation, translocation) and similar toxicological properties, and that uptake of soil metabolites is not relevant, an indicative chronic and acute consumer risk assessment for the representative use in potatoes resulted in exposure estimates well below the ADI and the ARfD, using EFSA PRIMo rev.2. The assessment is surrounded by a number of additional uncertainties (storage stability still to be addressed, number of residue trials low and not according to residue definition for risk assessment). Yet, as the identity of residues formed from the degrading known components in the neem extract, when applied to crops and/or the soil, is largely unknown, it is still not clear whether the lead component approach using azadirachtin A is appropriate for the consumer dietary risk assessment in general, and further clarification should be attempted to confirm the indicative risk assessment as appropriate. The RMS does not agree with this conclusion and considers the available data sufficient to finalise the consumer risk assessment.

The use on ornamentals requested in the application for amendment to the conditions of approval was not assessed in the residues section as not deemed relevant for consumer dietary exposure and risk assessment, provided ornamentals are not rotated with crops for human consumption.

4. Environmental fate and behaviour

The composition of the three different sources/technical materials named as azadirachtin (obtained from seed kernels of neem tree) has been clarified as part of the confirmatory data. It has been accepted that only components accounting for at least 10% of the majoritarian component (azadirachtin A) need to be considered for environmental exposure and risk assessment. Depending on the source, 3–10 components need to be addressed (see Appendix A for further details).

In the original dossier, there was one study providing some information on the route of degradation of some of the components of azadirachtin extracts in soil, performed with non-radiolabelled material containing azadirachtin A and azadirachtin B as main identified components. In this study, the only degradation proven is the one resulting from the hydrolysis of acetyl at C3 group in azadirachtin A (to yield major metabolite azadirachtin H* [max. 63%]). None of the products identified show any major transformation on the polycyclic structure of azadirachtin, and therefore, all known degradation products may be presumed to retain, at least in part, the biological properties attributed to this family of compounds. A data gap was identified for further investigation of the route of degradation of the azadirachtin extract active components to at least demonstrate that the polycyclic structure, common to all the active components, is broken down in soil under environmental conditions. No further studies have been provided as part of the confirmatory data package; therefore, the data gap is maintained for the

uses where exposure to soil cannot be excluded. This information is needed to satisfy the confirmatory data in order to finalise the residue definition and exposure to ground water. The RMS does not agree with this conclusion as considers this data gap out of the scope of the confirmatory data request.

Sufficient information is available on the rate of degradation of azadirachtin A (10 soils), azadirachtin B (seven soils), [redacted] (four soils), [redacted] (four soils), [redacted] (four soils), [redacted] (four soils), [redacted] (four soils) and [redacted] (four soils) in soil under aerobic conditions. Under these conditions azadirachtin A, azadirachtin B, [redacted] and [redacted] exhibit low to moderate persistence and [redacted] and [redacted] exhibited moderate persistence and [redacted] moderate to medium persistence. The degradation of component [redacted] was also investigated in this study. However, a data gap has been identified to clarify from which of the available sources the material used in rate of degradation study in soil Sala (2013) originates.

Information on the rate of degradation of the major metabolite azadirachtin H* is not sufficient to conclude on its persistence and no further information has been presented as part of the confirmatory data. Formation and degradation of this metabolite in soil have only been investigated in one soil. A data gap was identified to investigate the formation and degradation of this metabolite in at least two additional soils. The data is needed as part the confirmatory data since finalisation of residue definition and ground water risk assessment is specifically required by the Commission Implementing Directive 2011/44/EU. The RMS does not agree with this conclusion as considers this data gap out of the scope of the confirmatory data request.

No data on the degradation of azadirachtin extract components in soil under anaerobic conditions are available. These data are not deemed necessary to assess the representative use on potatoes. No data on the photolytic degradation of the azadirachtin extract active components in soil are available, and a data gap was identified.

Initial predicted environmental concentration in soil (PEC_{soil}) have been provided for the representative uses in field, based on the maximum amount established in the specification of the different components in the different sources.

Sufficient data on the adsorption/desorption of azadirachtin A in soil are available. The study performed to derive Freundlich behaviour used only three concentrations. Therefore, all available adsorption/desorption data have been retained to derive a K_{oc} to be used in the exposure assessment. According to these data, azadirachtin A may be classified as exhibiting low to very high mobility. The adsorption desorption endpoints for azadirachtin A may be used in the exposure assessment for azadirachtin B. A data gap was identified for a soil batch adsorption/desorption study with metabolite azadirachtin H* in at least three soils.

For the other specified components of azadirachtin extract: [redacted] and [redacted], the potential mobility in soil of azadirachtin components was estimated using OECD Guideline No. 121 by means of high-performance liquid chromatography (HPLC). This data can only be considered as tentative estimations subject to an error of at least 0.5 logarithmic units. Scientific Committee on Plants specifically recommended not using this method as alternative to the batch adsorption method in cases the later was not applicable (European Commission, 2002d). In this case, at least for compounds [redacted] and [redacted] does not seem to be any justification for not performing standard OECD 106 test since both substances are commercially available and sufficiently stable in soil and water. Therefore, a data gap is identified for appropriate estimation of adsorption in soil of [redacted], and [redacted] and [redacted]. The RMS does not agree with this conclusion as consider the available data sufficient to characterise the mobility of azadirachtin components.

Both azadirachtin A and B hydrolyse in water (likely to form the C3 hydroxyl derivative, azadirachtin H*) at environmental pHs (pH 4–8). Hydrolysis is faster at more alkaline pHs. No information is available on the hydrolysis of the other known active azadirachtin extract components, and therefore, a data gap was identified. Similarly, no experimental information is available on the aqueous photolysis of any of the known active components of azadirachtin extract, and therefore, a data gap was identified.

No guideline water/sediment study is available for the azadirachtin extract active components. A natural water degradation study is available for azadirachtin A and azadirachtin B, and an outdoor study with a water/forest sediment system is available for azadirachtin A. In the confirmatory data package, some additional information from scientific literature on persistence of azadirachtin A and B in an outdoor mesocosm and a forest pond in Canada is provided and considered supplemental by the RMS.

The degradation half-life observed in the water system study, presented in the first submission, was used as the endpoint to represent dissipation from water in the calculation of predicted environmental concentration in surface water (PEC_{sw}) for azadirachtin A for the field use in potatoes. These calculations were done following the FOCUS SW (FOCUS 2001)[3] scheme up to step 4 assuming mitigation of spray drift and run-off. However, risk managers and others may wish to note that whilst run-off mitigation is included in the step 4 calculations available, the FOCUS (FOCUS, 2007) report acknowledges that for substances with K_{Foc} < 2,000 mL/g (i.e. azadirachtin A), 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.

PEC_{sw} for the field use in potatoes, using FOCUS SW (FOCUS, 2001) up to Step 3, have been derived for these other components in the dossier using the soils geometric mean DT_{50} measured in the rate study submitted, the K_{oc} estimated by the HPLC study and worst-case half-lives of 1,000 days for water and sediment. An application rate of 25 g/ha for each component has been assumed, and then, the result corrected for the actual maximum amount in the specifications of the different sources. This is expected to result in tentative worst-case PEC_{SW} applicable to the environmental the risk assessment. For the use simulated, azadirachtin A resulted in the highest PEC for most of the scenarios applicable to potatoes in northern EU (D3 ditch, D4 pond, D4 stream and R1 stream) with [redacted] resulting in higher PEC_{SW} for R1 pond scenario. Since the relative proportion of the components in surface water may vary depending on the scenarios and uses considered, all components need in principle to be retained for the risk assessment of aquatic environment (no lead compound approach possible). Nevertheless, MSs risk assessment experts may wish to discuss in the future on the possibility of reducing the number of compounds that need specific calculation by adequate bridging of results from a reduced number of representative components. EFSA noted that predicted environmental concentration in sediment (PEC_{sed}) are not reported; therefore, a data gap is identified for PEC_{sed} to be calculated and reported for all the active components of azadirachtin and for updating the PEC_{SW} calculations once fully reliable adsorption/desorption parameters in soil for all components are determined.

Neither data nor aquatic exposure assessment are available for the major soil metabolite azadirachtin H* (likely to be also produced by hydrolysis in water) nor for any other metabolite resulting from the degradation of azadirachtin components. A data gap was identified to address the water exposure assessment for the environmental metabolites of azadirachtin components, in particular for major soil metabolite azadirachtin H*.

The potential for groundwater contamination by azadirachtin A was addressed by standard FOCUS GW calculations (FOCUS, 2000)[4] with the PEARL and PELMO models. The limit of 0.1 µg/L is not exceeded for any of the simulated scenarios. As part of the confirmatory package, five of the active components of azadirachtin were identified based on their persistence and soil adsorption properties as more critical in terms of potential leaching: azadirachtina A, azadirachtin B, [redacted] and [redacted] (it is noted component [redacted] is present at levels < 10% in relation to azadirachtin A, and it can be accepted more as an impurity than a true major component). For these compounds, the potential leaching was tentatively calculated (see issues with adsorption input parameters used above) with the FOCUS GW models PELMO 5.5.3 and FOCUS PEARL 4.4.4. for only one part of the scenarios relevant to the representative use in potatoes arguing that only use in northern EU was supported by the applicant. However, FOCUS scenarios are constructed to represent different vulnerable situations in Europe and all nine scenarios may in principle cover geoclimatic situations present in northern and southern zones. Therefore, a data gap has been identified to complete the assessment with all the scenarios relevant to potatoes. In addition, it is noted that application rates simulated for the 'representative' components are calculated on basis of their actual presence in the technical material; however, the simulations intend to cover the situation of other components of similar properties that may occur at higher amounts than the component selected for the simulations. Therefore, new calculations are needed simulating the maximum amount of the major components covered by the representative ones, using fully reliable soil adsorption parameters for all components.

Potential groundwater contamination by the major soil metabolite azadirachtin H* was only been preliminarily assessed by the RMS on the basis of a single soil half-life and an assumed K_{oc} = 10 mL/g with FOCUS GW (using PEARL and PELMO). The values obtained do not enable to exclude the

[3] Simulations utilised a Q10 of 2.58 (EFSA 2007) and Walker Equation coefficient of 0.7.
[4] Simulations complied with EFSA (2004) and utilised a Q10 of 2.58 (EFSA 2007) and Walker Equation coefficient of 0.7.

potential for leaching and confirm the need for further data to finalise the groundwater exposure assessment for this metabolite. Potential groundwater contamination by potential metabolites of other active components has not been assessed, and therefore, a data gap was identified. Taking into account the active substance definition, it is not clear to EFSA if the parametric drinking water limit of 0.1 μg/L applies to each of the individual active components or to the sum of all of them. In the case that it is decided that 0.1 μg/L is applicable to the individual components, then Council Directive 98/83/EC[5] prescribes that the limit of 0.5 μg/L would need to be taken into consideration for the sum of all the active components.

In conclusion, the confirmatory data request with respect to the groundwater assessment for the representative uses for which authorisation was granted in Commission Implementing Directive 2011/44/EU cannot be considered completed or satisfied with the available information provided. Further data would also be needed to clarify the residue definitions for risk assessment and monitoring of the different environmental compartments.

For the new use proposed in greenhouse on ornamentals in artificial soils, initial PEC_{SW} for the azadirachtin A component was calculated assuming that 0.1% (aeric mass %) of the application rate is deposited on surface water. It should be noted that only when the peak maximum is the result of a spray drift event, the initial amount of the other components and the whole extract reaching the surface water can be estimated. Applicant proposed just to correct values obtained for scenarios D3 and D4 already calculated for potato uses in northern EU. Since the use is in greenhouse for ornamentals, the restriction of the assessment to only these scenarios is not justified. Therefore, a data gap is identified for the applicant to complete the aquatic risk assessment for all EU scenarios relevant for the proposed use in greenhouse (or to simply calculate PEC_{SW} resulting from a 0.1% emission on standard water bodies).

No PEC_{soil} or predicted environmental concentration in ground water (PEC_{GW}) was provided for this new use since it is assumed that the greenhouse is a permanent structure with artificial substrate.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a–c), SETAC (2001).

Azadirachtin was discussed in the PRAPeR 77 ecotoxicology experts' meeting in June 2010.

There are three aspects to the current conclusion on the ecotoxicology assessment, namely, whether the confirmatory data requirement is addressed, whether the conclusion on the additional use to ornamentals in permanent greenhouses and the additional data included in the confirmatory data addendum changes the previous conclusion for the representative use to potatoes. Each point has been considered separately.

1) Updated risk assessment for the representative use to potatoes

The acute and long-term risk to birds and mammals was assessed as low in a first-tier risk assessment according to SANCO/4145/2000 (European Commission, 2002c). The long-term reproduction endpoint from the two-generation rat study (no observed effect level (NOEL) = 13.7 mg azadirachtin A/kg bw per day) was used in the original risk assessment for mammals. This was questioned during the first peer review (EFSA, 2011b) since a lower endpoint was observed in a teratogenicity study. In the meeting of experts (PRAPeR 77), it was decided that the lower endpoint from the teratogenicity study (NOEL = 8.3 mg azadirachtin A/kg bw per day) should be used in the risk assessment. The recalculated toxicity exposure ratios (TERs) were well above the assessment factor of 5. The risk was assessed according to SANCO/4145/2000 (European Commission, 2002a–d) based on a medium herbivorous mammal. It was noted in the meeting that shrews may also be found in potatoes fields. It can be expected that TERs for shrews would exceed the assessment factor and hence are covered by the available risk assessment. Overall, the risk to birds and mammals is expected to be low for the representative use evaluated. The available risk assessments were performed in terms of azadirachtin A as the lead component. However, it is noted that the toxicity endpoints were derived from studies using total azadirachtin. Quantification of the other components cannot be verified owing to the different sources used in the toxicity studies. Nevertheless, when considering the margin of safety obtained in the available risk assessments, it is considered that the risk assessments performed for azadirachtin A are sufficient to address the risk from total azadirachtin.

[5] Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption, OJ L 330 5.12, 1998. p.32

Azadirachtin is very toxic to aquatic organisms. The lowest endpoints were observed for fish (acute LC_{50} = 0.048 mg azadirachtin A/L, chronic no observed effect concentration (NOEC) = 0.0047 mg azadirachtin A/L) and aquatic insects (chronic NOEC = 0.0016 mg azadirachtin A/L). The TERs exceeded the assessment factor for all $FOCUS_{sw}$ step 3 scenarios except the part scenario R1 stream. A $FOCUS_{sw}$ step 4 calculation including a 10-m no-spray buffer zone resulted in a TER of 15 for the part scenario R1 stream. Vegetative buffer strips may not be effective to mitigate run-off of mobile substances such as azadirachtin A (see Section 4). Overall, it was concluded that the risk from azadirachtin A to the aquatic environment was low, except for the part scenario R1 stream, for which risk mitigation was suggested. The available risk assessments were performed in terms of azadirachtin A. To support this approach, acute toxicity data for the most sensitive aquatic species, *Chironomus riparius*, were submitted for each of the individual components in azadirachtin. The data indicated that all components were of comparable or lower toxicity than azadirachtin A. A risk assessment was also presented which indicated that the individual components were unlikely to pose an acute risk to *C. riparius*. However, EFSA notes that the aquatic risk assessment is driven by the chronic toxicity to *C. riparius*. Furthermore, the exposure assessment for compounds other than azadirachtin A remains open (see Section 4). Consequently, for the aquatic risk assessment, it has not been demonstrated that the lead component approach, using azadirachtin A, is appropriate (data gap). The RMS does not agree with this conclusion as they consider that the available acute risk assessment for the individual components is sufficient.

The risk assessment for non-target arthropods was discussed in the expert meeting (PRAPeR 77). The risk was assessed as low for *Typhlodromus pyri, Aphidius rhopalosiphi* and *Poecilus cupreus. Coccinella septempunctata* and *Chrysoperla carnea* were clearly more sensitive, and an initial impact on populations of sensitive arthropod species can be expected based on the observations in laboratory studies. However, higher tier data suggest that recolonisation of the in-field area is possible within 1 year. An in-field no-spray buffer zone of 5 m is required to protect sensitive arthropod populations in the off-field area. The available risk assessments were performed in terms of azadirachtin A. To support this approach, data demonstrating the toxicity of the individual components to *C. carnea* were submitted. The data indicated that azadirachtin B and [redacted] were of greater toxicity than azadirachtin A. The RMS concluded that the risks from the individual components were addressed by the risk assessment for azadirachtin A given that azadirachtin A is present in higher concentrations in the technical material. However, it was not demonstrated whether the test material used in the key non-target arthropod studies contained sufficient amounts of azadirachtin B, [redacted] and [redacted] to conclude that the previous risk assessment was appropriate (data gap).

The MS experts discussed whether the effects of potential degradation products of azadirachtin would be covered by the study with the soil-dwelling mite *Hypoaspis aculeifer*. The mites were exposed for 14 days to fresh treated soil (9,794 mg NeemAzal/kg soil corresponding to 3,000 mg azadirachtin A/kg soil) and after ageing of the treated soil. Significant adverse effects were observed after exposure to fresh residues and after 2 days of ageing, but no adverse effects on mortality or reproduction were observed after 7 days of ageing of residues. The experts considered it likely that degradation products were present after ageing of residues and that the residues would not pose a high risk to soil-dwelling mites. Uncertainty remains since no measurements of residues were performed. However, since the tested concentrations were more than four orders of magnitude greater than the initial PEC_{soil} a large margin of safety is indicated and the risk to soil-dwelling mites was considered to be low. The risk to earthworms and soil macroorganisms from azadirachtin A and the extracts was assessed as low on the basis of initial PEC_{soil} values. However, no information was available for the individual compounds of the extract or degradation products, which adds uncertainty to the outcome of the risk assessment on a long-term time scale. The study with soil-dwelling mites gave an indication that ageing of residues would not lead to an increase of the risk. Overall, it is considered as unlikely that the risk to soil-dwelling organisms would be high. As discussed in Section 4, it was concluded that the confirmatory data was not sufficient to confirm the lead component approach, using azadirachtin A, for the exposure assessment. Consequently, it was not possible to finalise the risk assessment for soil organisms and further information on the fate and behaviour and toxicity of the individual compounds is needed to confirm the risk assessment for soil-dwelling organisms and to finalise the relevance assessment of metabolites. The RMS does not agree with this conclusion and believes that the risk assessment performed only for azadirachtin A is sufficient to conclude a low risk from the total azadirachtin.

The risk to bees, soil microorganisms, non-target plants and biological methods of sewage treatment were assessed as low. The assessments were considered to provide sufficient margins of safety to address the uncertainty of performing a lead component risk assessment with azadirachtin A.

2) Confirmatory data

The confirmatory data requirement was to consider the appropriateness of the environmental residue definition in soil and water. The previous risk assessment for water and soil organisms was performed on azadirachtin A as the lead component in azadirachtin. Consequently, only azadirachtin A was listed in the list of ecotoxicologically relevant compounds. As the risk assessments for soil organisms and aquatic organisms could not be finalised, it is also not possible to confirm that only azadirachtin A is the only substance that should be regarded as ecotoxicologically relevant. Therefore, the confirmatory data requirement remains open.

3) Use to ornamentals in glasshouses

The risk assessment provided with the post-approval application for the use on ornamentals in greenhouse assumes that the greenhouse is a permanent structure. On this basis, the exposure for non-target organisms was excluded, except for aquatic organisms. As the aquatic exposure assessment for was not agreed (see Section 4), the risk assessment for aquatic organisms could not be finalised and a data gap was identified.

It is noted that, in case of uses in greenhouse as open protected structures, the exposure to the non-target organisms cannot be excluded and a risk assessment would be required as for the field uses. The representative use on ornamentals is a worst-case GAP with respect to the previous use evaluated for the EU approval. Therefore, a risk assessment should be performed; this is particular relevant for the aquatic organisms and non-target arthropods, where mitigation measures were needed for the representative use in potatoes.

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
Azadirachtin A	Low to moderate ($DT_{50\ 20°C}$ = 1.7–27 days)	The risk to earthworms, soil-dwelling micro- and macroorganisms was assessed as low
Azadirachtin B	Low to moderate ($DT_{50\ 20°C}$ = 5.9–37.3 days)	Risk assessment open owing to the lack of exposure assessment
[redacted]	Low to moderate ($DT_{50\ 20°C}$ = 6.2–36.5 days)	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment
[redacted]	Moderate ($DT_{50\ 20°C}$ = 10.0–63.1 days)	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment
[redacted]	Moderate ($DT_{50\ 20°C}$ = 12.5–40.3 days)	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment
[redacted]	Low to moderate ($DT_{50\ 20°C}$ = 3.8–11.0 days)	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment
[redacted]	Moderate ($DT_{50\ 20°C}$ = 14.7–34.4 days)	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment
[redacted]	Low to moderate ($DT_{50\ 20°C}$ = 1.7–19.4 d)	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment
[redacted]	Moderate ($DT_{50\ 20°C}$ = 15.5–30.4 days)	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment
[redacted]	Moderate to medium ($DT_{50\ 20°C}$ = 12.4–84.8 days)	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment
Azadirachtin H*	Available data are not sufficient to finalise the risk assessment	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment
Other metabolites of active components.	No data available	Risk assessment open, for the representative use to potatoes, owing to the lack of exposure assessment

DT_{50}: period required for 50% dissipation.

Table 2: Ground water

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
Azadirachtin A	Low to very high mobile (K_{oc} = 20.6–875.1 mL/g)	FOCUS GW: not for four of the relevant scenarios to potatoes. Data gap identified to finalise the assessment for the other relevant groundwater scenarios for potatoes	Yes	No data available; not possible to assess the toxicity of azadirachtin A *per se*
Azadirachtin B	No information available Azadirachtin A adsorption/desorption endpoints are considered applicable to azadirachtin B	FOCUS GW: not for four of the scenarios. Data gap identified to finalise the assessment for the other relevant groundwater scenarios for potatoes	No data available Data gap	No data available; not possible to assess the toxicity of azadirachtin B *per se*
[redacted]	No reliable information available Tentative estimation available based on OECD121 (HPLC method)	Available data in the resubmission dossier are neither fully reliable nor complete Data gaps identified	No data available Data gap	No data available; not possible to assess the toxicity of [redacted] *per se*
[redacted]	No reliable information available Tentative estimation available based on OECD121 (HPLC method)	Available data in the resubmission dossier are neither fully reliable nor complete Data gaps identified	No data available Data gap	No data available; not possible to assess the toxicity of [redacted] *per se*
[redacted]	No reliable information available Tentative estimation available based on OECD121 (HPLC method)	Available data in the resubmission dossier are neither fully reliable nor complete Data gaps identified	No data available Data gap	No data available; not possible to assess the toxicity of [redacted] *per se*
[redacted]	No reliable information available Tentative estimation available based on OECD121 (HPLC method)	Available data in the resubmission dossier are neither fully reliable nor complete Data gaps identified	No data available Data gap	No data available; not possible to assess the toxicity of [redacted] *per se*
[redacted]	No reliable information available Tentative estimation available based on OECD121 (HPLC method)	Available data in the resubmission dossier are neither fully reliable nor complete Data gaps identified	No data available Data gap	No data available; not possible to assess the toxicity of [redacted] *per se*
[redacted]	No reliable information available Tentative estimation available based on OECD121 (HPLC method)	Available data in the resubmission dossier are neither fully reliable nor complete Data gaps identified	No data available Data gap	No data available; not possible to assess the toxicity of [redacted] *per se*

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
[redacted]	No reliable information available Tentative estimation available based on OECD121 (HPLC method)	Available data in the resubmission dossier are neither fully reliable nor complete Data gaps identified	No data available Data gap	No data available; not possible to assess the toxicity of [redacted] *per se*
[redacted]	No reliable information available Tentative estimation available based on OECD121 (HPLC method)	Available data in the resubmission dossier are neither fully reliable nor complete Data gaps identified	No data available Data gap	No data available; not possible to assess the toxicity of [redacted] *per se*
Azadirachtin H*	No information available Data gap identified. Assumed to be more mobile than azadirachtin A. K_{oc} = 10 mL/g has been used as default for a preliminary assessment.	Preliminary data available Data gap The FOCUS preliminary assessment shows that groundwater concentrations are not expected to be negligible and that safe use may not be presumed without further data	No data available Data gap	No data available; not possible to assess the toxicity of azadirachtin H* *per se*
Other metabolites of active components	No information available	No data available Data gap	No data available Data gap	No data available

HPLC: high-performance liquid chromatography.
(a): At least one FOCUS scenario or relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Azadirachtin A	Very toxic to aquatic organisms (fish LC_{50} = 0.048 mg azadirachtin A/L and aquatic insects chronic NOEC = 0.0016 mg azadirachtin A/L). For the representative use to potatoes, the lowest TERs were above the assessment factor for 2 of 3 full FOCUS step 3 scenarios. One part scenario (R1 stream) needed risk mitigation comparable to a 10 m no-spray buffer zone
Azadirachtin B	Risk assessment open owing to the lack of exposure assessment
[redacted]	Risk assessment open owing to the lack of exposure assessment
[redacted]	Risk assessment open owing to the lack of exposure assessment
[redacted]	Risk assessment open owing to the lack of exposure assessment
[redacted]	Risk assessment open owing to the lack of exposure assessment
[redacted]	Risk assessment open owing to the lack of exposure assessment
[redacted]	Risk assessment open owing to the lack of exposure assessment
[redacted]	Risk assessment open owing to the lack of exposure assessment
[redacted]	Risk assessment open owing to the lack of exposure assessment
Azadirachtin H* (from soil)	Risk assessment open owing to the lack of exposure assessment
Other soil and water/sediment metabolites of active components.	Risk assessment open owing to the lack of exposure assessment

LC: liquid chromatography; TER: toxicity exposure ratio; NOEC: no observed effect concentration.

Table 4: Air

Compound (name and/or code)	Toxicology
Azadirachtin extract active components (No conversion factor from azadiracthin A (used as a marker for analytical purposes) and the other components to the bulk azadirachtin extract is available. Such a conversion factor would need to consider the different specifications proposed for the different technical materials.)	Rat LC_{50} inhalation > 0.72 mg Trifolio-M extract/L air (4 h, whole body) – no classification proposed Rat LC_{50} inhalation > 2.45 mg Sipcam extract/L air (4 h, whole body) – no classification proposed

LC: liquid chromatography.

7. Data gaps

This is a complete list of the data gaps identified during the peer review process, including those areas where 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 the Regulation concerning information on potentially harmful effects).

- A search of the scientific peer-reviewed open literature relevant to the scope of the application for amendment to the conditions of approval, dealing with side effects on health, the environment and non-target species and published within the last 10 years before the date of submission of dossier, to be conducted and reported in accordance with the Guidance of EFSA on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011a; relevant for all representative uses evaluated; submission date proposed by the applicant: unknown).
- Information on the composition of the batches used in the toxicological studies conducted with the Mitsui source (relevant for all representative uses evaluated with the Mitsui source; submission date proposed by the applicant: unknown; see Section 2).
- Information on the toxicological profile/relevance of the different components/impurities/ by-products present in the technical specification of the three azadirachtin extracts (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Demonstration of integrity of residues for all analytes over the entire period of sample storage in the lettuce residue trial (relevant for potato uses; submission date proposed by the applicant: immediately available upon request; see Section 3).
- Further investigation of the route of degradation of the azadirachtin extract active components in soil to identify other potential major metabolites and to at least demonstrate that the polycyclic structure, common to all the active components, is broken down in soil under environmental conditions (relevant for use in potatoes; submission date proposed by the applicant: unknown; see Sections 3 and 4).
- Applicants to clarify the origin/source of the azadirachtin used in the investigation of the rate of degradation of azadirachtin components in soil (relevant for use in potatoes; submission date proposed by the applicant: unknown; see Section 4).
- The formation and degradation of azadirachtin H* (major soil metabolite product of desacetylation of azadirachtin A) to be investigated in two additional soils (relevant for use in potatoes; submission date proposed by the applicant: unknown; see Section 4).
- Information on the photolysis of the azadirachtin extract active components in soil (relevant for use in potato; submission date proposed by the applicant: unknown; see Section 4).
- Adsorption/desorption study in at least three soils with major soil metabolite azadirachtin H* (relevant for use in potato; submission date proposed by the applicant: unknown; see Section 4).
- The mobility in soil of the azadirachtin extract active components: [redacted] (four soils) and [redacted] (relevant for use in potatoes; submission date proposed by the applicant: unknown, see Section 4).
- The aqueous hydrolysis of the azadirachtin extract active components: [redacted] (four soils) and [redacted] (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 4).
- The aqueous photolysis of the azadirachtin extract active components [redacted] (four soils) and [redacted] to be addressed (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 4).
- Aquatic exposure assessment for the known active components of azadirachtin using fully reliable adsorption/desorption input parameters, it is noted that these exposure estimations need to address as well exposure to sediment and be completed for all scenarios relevant to the potatoes use in field in northern Europe and the greenhouse use (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 4).
- Aquatic exposure assessment for the environmental metabolites of azadirachtin components, in particular for major soil metabolite azadirachtin H* (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 4).

- Groundwater exposure assessment of azadirachtin components using fully reliable absorption/ desorption input parameters and application rates corresponding to the amounts specified in the different sources and for all scenarios relevant to potatoes representative use. If envelope approach with a selected number of components is employed for the modelling exercise, it should be guaranteed that the maximum application rate of all components represented by the selected ones is covered by the calculations (relevant for use in potatoes; submission date proposed by the applicant: unknown; see Section 4).
- Groundwater exposure assessment for the soil metabolites of azadirachtin components (including azadirachtin H*), including an assessment of pesticidal activity and ecotoxicological activity to finalise the groundwater metabolite relevance assessment as applicable (relevant for use in potatoes; submission date proposed by the applicant: unknown; see Section 4).
- Further information is needed to confirm the appropriateness of the lead component approach using azadirachtin A for the risk assessments for soil organisms and aquatic organisms. This information is also needed to confirm that only azadirachtin A should be considered as ecotoxicologically relevant in soil and water (relevant for the representative use to potatoes; submission date proposed by the applicant: unknown; see Section 5). Information on the batches used in the studies performed with non-target arthropods is needed. It should be demonstrated that azadirachtin B, [redacted] and [redacted] were present in sufficient amounts to confirm that the available risk assessment presented in terms of azadirachtin A is sufficiently protective (relevant for the representative use to potatoes; submission date proposed by the applicant: unknown; see Section 5).
- The risk assessment for aquatic organisms should be updated once the exposure assessment to surface water has been finalised (relevant for the representative use to ornamentals in greenhouses; 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

- For the representative use to potatoes, an in-field no-spray buffer zone of 5 m is needed to protect sensitive arthropod species (see Section 5).
- For the representative use to potatoes, risk mitigation comparable to a no-spray buffer zone of 10 m is necessary to protect aquatic species from exposure to azadirachtin A under environmental conditions represented by FOCUS scenario R1 stream (see Section 5).
- For the use on ornamentals in greenhouse only, use in artificial substrate and permanent greenhouses has been assessed (see Sections 2, 4 and 5).

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where 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 the Regulation and as set out in Commission Regulation (EU) No 546/2011[6] and where 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 the Regulation.

1) There is no information to conclude if the batches used in the toxicological studies with the Mitsui source are representative of the respective technical specification.
2) The relevance of the impurities and by-products of the three azadirachtin extracts (from the Trifolio-M, Sipcam and Mitsui sources) are unknown; the main compound(s) responsible for the toxicological properties of the azadirachtin extracts were not identified.

[6] 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.

3) The nature of residues in plants from application of the neem extracts is unknown. It is, therefore, not possible to finalise the consumer risk assessment for the representative use on potatoes
4) The environmental exposure assessment, including groundwater exposure, cannot be finalised.
5) The risk assessment for aquatic organisms (all representative uses), soil organisms and non-target arthropods (representative use on potatoes only) cannot be finalised with the available information.

9.2. Critical areas of concern

An issue is listed as a critical area of concern where 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 the Regulation and as set out in Commission Regulation (EU) No 546/2011, and where this assessment does not permit to conclude 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 where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude 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 the Regulation.

- 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.)

All columns for the use in potatoes are grey as the technical material specification proposed for Mitsui (ATI 720) source was not comparable to the material used in the batches used to derive the toxicological reference values.

Table 5: Overview of concerns

Representative use		Northern Europe Potato 'NeemAzal-T/S'	Northern Europe Potato 'Oikos'	Northern and central Europe Ornamentals on artificial soil
Operator risk	Risk identified			
	Assessment not finalised			
Worker risk	Risk identified			
	Assessment not finalised			
Resident/ bystander risk	Risk identified			
	Assessment not finalised			
Consumer risk	Risk identified			
	Assessment not finalised	X[3]	X[3]	
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	X[5]	X[5]	

Representative use		Northern Europe Potato 'NeemAzal-T/S'	Northern Europe Potato 'Oikos'	Northern and central Europe Ornamentals on artificial soil
Risk to aquatic organisms	Risk identified			
	Assessment not finalised	X[5]	X[5]	X[5]
Groundwater exposure to active substance	Legal parametric value breached			
	Assessment not finalised	X[4]	X[4]	Not relevant
Groundwater exposure to metabolites	Legal parametric value breached[(a)]			
	Parametric value of 10 μg/L[(b)] breached			
	Assessment not finalised	X[4]	X[4]	Not relevant
Comments/ Remarks				Ornamentals in high technology permanent greenhouse in artificial substrate (no soil exposure)

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections.
(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December.
(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003.

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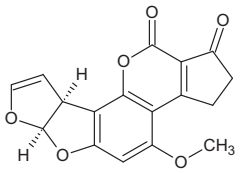
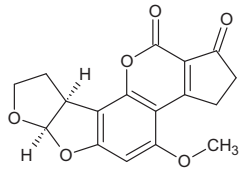
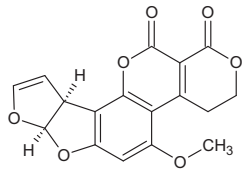
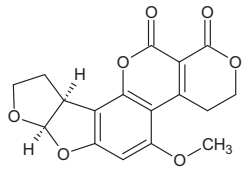
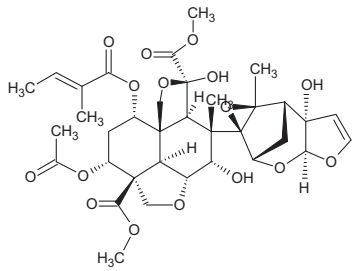
Abbreviations

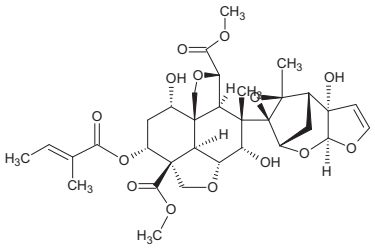
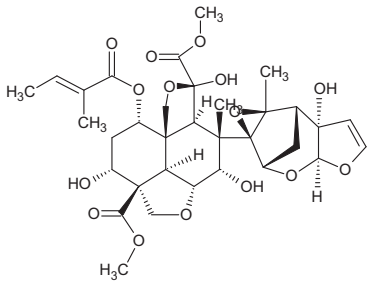
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
bw	body weight
CF	conversion factor
CIPAC	Collaborative International Pesticides Analytical Council Limited
DAR	draft assessment report
DT_{50}	period required for 50% dissipation (define method of estimation)
EC	emulsifiable concentrate
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
HPLC	high-performance liquid chromatography
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on 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_{Foc}	Freundlich organic carbon adsorption coefficient
LC_{50}	lethal concentration, median
LOQ	limit of quantification
MRL	maximum residue level
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
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
SMILES	simplified molecular-input line-entry system
TER	toxicity exposure ratio
TK	technical concentrate
WHO	World Health Organization

Appendix A – List of endpoints 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.2018.5234

Appendix B – Used compound code(s)

Code/trivial name	IUPAC name/SMILES notation/InChiKey[a]	Structural formula[b]
Aflatoxin B_1	(6a*R*,9a*S*)-4-methoxy-2,3,6a,9a-tetrahydrocyclopenta[*c*]furo[3′,2′:4,5]furo[2,3-*h*][1]benzopyran-1,11-dione O=C2Oc1c4c(cc(OC)c1C=3CCC(=O)C2 = 3)O[C@H]5OC=C[C@@H]45 OQIQSTLJSLGHID-WNWIJWBNSA-N	
Aflatoxin B_2	(6a*R*,9a*S*)-4-methoxy-2,3,6a,8,9,9a-hexahydrocyclopenta[*c*]furo[3′,2′:4,5]furo[2,3-*h*][1]benzopyran-1,11-dione O=C2Oc1c4c(cc(OC)c1C=3CCC(=O)C2 = 3)O[C@H]5OCC[C@@H]45 WWSYXEZEXMQWHT-WNWIJWBNSA-N	
Aflatoxin G_1	(7a*R*,10a*S*)-5-methoxy-3,4,7a,10a-tetrahydro-1*H*,12*H*-furo[3′,2′:4,5]furo[2,3-*h*]pyrano[3,4-*c*][1]benzopyran-1,12-dione O=C2Oc1c4c(cc(OC)c1C=3CCOC(=O)C2 = 3)O[C@H]5OC=C[C@@H]45 XWIYFDMXXLINPU-WNWIJWBNSA-N	
Aflatoxin G_2	(7a*R*,10a*S*)-5-methoxy-3,4,7a,9,10,10a-hexahydro-1*H*,12*H*-furo[3′,2′:4,5]furo[2,3-*h*]pyrano[3,4-*c*][1]benzopyran-1,12-dione O=C2Oc1c4c(cc(OC)c1C=3CCOC(=O)C2 = 3)O[C@H]5OCC[C@@H]45 WPCVRWVBBXIRMA-WNWIJWBNSA-N	
Azadirachtin A	dimethyl (2a*R*,3*S*,4*S*,4a*R*,5*S*,7a*S*,8*S*,10*R*,10a*S*,10b*R*)-10-(acetyloxy)-3,5-dihydroxy-4-[(1a*R*,2*S*,3a*S*,6a*S*,7*S*,7a*S*)-6a-hydroxy-7a-methyl-3a,6a,7,7a-tetrahydro-2,7-methanofuro[2,3-*b*]oxireno[*e*]oxepin-1a(2*H*)-yl]-4-methyl-8-{[(2*E*)-2-methylbut-2-enoyl]oxy}octahydro-1*H*-naphtho[1,8a-*c*:4,5-*b*′*c*′]difuran-5,10a(8*H*)-dicarboxylate C\C=C(/C)C(=O)O[C@H]5C[C@@H](OC(C)=O)[C@]7(CO[C@H]6[C@@H](O)[C@@](C)([C@@]34O[C@@]4(C)[C@H]1C[C@@H]3O[C@@H]2OC=C[C@]12O)[C@@H]8[C@](O)(OC[C@@]58[C@@H]67)C(=O)OC)C(=O)OC FTNJWQUOZFUQQJ-NDAWSKJSSA-N	

Code/trivial name	IUPAC name/SMILES notation/InChiKey[a]	Structural formula[b]
Azadirachtin B	dimethyl (2a*R*,3*S*,4*S*,4a*R*,5*S*,7a*S*,8*S*,10*R*,10a*S*,10b*R*)-3,8-dihydroxy-4-[(1a*R*,2*S*,3a*S*,6a*S*,7*S*,7a*S*)-6a-hydroxy-7a-methyl-3a,6a,7,7a-tetrahydro-2,7-methanofuro[2,3-*b*]oxireno[*e*]oxepin-1a(2*H*)-yl]-4-methyl-10-{[(2*E*)-2-methylbut-2-enoyl]oxy}octahydro-1*H*,7*H*-naphtho[1,8a-*c*:4,5-*b'c'*]difuran-5,10a(8*H*)-dicarboxylate C\C=C(/C)C(=O)O[C@@H]2C[C@H](O)[C@@]41CO[C@H](C(=O)OC)[C@H]1[C@@](C)([C@H](O)[C@@H]3OC[C@@]2(C(=O)OC)[C@H]34)[C@@]78O[C@@]8(C)[C@H]5C[C@@H]7O[C@@H]6OC=C[C@]56O USRBWQQLHKQWAV-ZGKQVQOISA-N	
[redacted]	[redacted]	[redacted]
Azadirachtin H*	dimethyl (2a*R*,3*S*,4*S*,4a*R*,5*S*,7a*S*,8*S*,10*R*,10a*S*,10b*R*)-3,5,10-trihydroxy-4-[(1a*R*,2*S*,3a*S*,6a*S*,7*S*,7a*S*)-6a-hydroxy-7a-methyl-3a,6a,7,7a-tetrahydro-2,7-methanofuro[2,3-b]oxireno[*e*]oxepin-1a(2*H*)-yl]-4-methyl-8-{[(2*E*)-2-methylbut-2-enoyl]oxy}octahydro-1*H*-naphtho[1,8a-*c*:4,5-*b'c'*]difuran-5,10a(8*H*)-dicarboxylate C\C=C(/C)C(=O)O[C@H]5C[C@@H](O)[C@]7(CO[C@H]6[C@@H](O)[C@@](C)([C@@]34O[C@@]4(C)[C@H]1C[C@@H]3O[C@@H]2OC=C[C@]12O)[C@@H]8[C@](O)(OC[C@@]58[C@@H]67)C(=O)OC)C(=O)OC GLAJZJRWMNNYEH-QMIGGIAWSA-N	
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Code/trivial name	IUPAC name/SMILES notation/InChiKey[a]	Structural formula[b]
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Code/trivial name	IUPAC name/SMILES notation/InChiKey[a]	Structural formula[b]
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(a): ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 Dec 2014).
(b): ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 Dec 2014).