



EUROPEAN COMMISSION
HEALTH & CONSUMERS DIRECTORATE-GENERAL

Directorate E – Safety of the food chain
Unit E.3 - Chemicals, contaminants and pesticides

Azadirachtin
SANCO/10311/2011 final
11 March 2011

Review report for the active substance **azadirachtin**
finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on
11 March 2011
in view of the inclusion of azadirachtin to Annex I of Directive 91/414/EEC

1. Procedure followed for the re-evaluation process

This review report has been established as a result of the re-evaluation of azadirachtin, made in the context of a new application by the data submitter after the non-inclusion of this substance.

Azadirachtin is a substance that was covered by the fourth stage of the work programme for review of existing active substances provided for in Article 8(2) of Directive 91/414/EEC concerning the placing of plant protection products on the market, with a view to the possible inclusion of this substance in Annex I to the Directive.

Article 24(e) of Commission Regulation (EC) No 2229/2004 laying down detailed rules for the implementation of the fourth stage offered the possibility for the notifier to withdraw, under specific conditions, its support for the active substance. All notifiers withdrew their support and azadirachtin was not included through Commission Decision 2008/941/EC¹.

In accordance with Article 13 of Regulation (EC) No 33/2008, the applicants Trifolio-M GmbH, sipcam S.p.a. and Mitsui Agriscience International S.A/B.V presented, a request to Germany, the rapporteur Member State, for a new application aiming at Annex I inclusion of the substance.

Germany finalised in December 2009 its examination, in the form of an additional report to the original Draft Assessment Report. This Report was sent to the Commission and the European Food Safety Authority on 10 December 2009 and included a recommendation as to include azadirachtin in Annex I for the supported uses.

The EFSA organised the consultation on the draft assessment report and, in accordance with the provisions of Article 19 of Regulation (EC) No 33/2008, on the additional report by all the Member States as well as by Azadirachtin applicants on 11 December 2009 by making it available.

In accordance with the provisions of Article 20 of Regulation (EC) No 33/2008, the Commission asked EFSA to organise a focused consultation of scientific experts from a certain number of

¹ OJ No L 335, 13.12.2008, p. 91.

Member States, to review the additional report, draft assessment report and the comments received thereon (peer review) and to deliver its conclusion.

In accordance with the provisions of Article 20 of Regulation (EC) No 33/2008 the EFSA sent to the Commission its conclusion on the risk assessment [Conclusions on the peer review of the pesticide risk assessment of the active substance azadirachtin (issued on 11 October 2010)²]. This conclusion refers to background document A (draft assessment report and additional report) and background document B (EFSA peer review report).

In accordance with the provisions of Article 21 of Regulation (EC) No 33/2008, the Commission referred a draft review report to the Standing Committee on the Food Chain and Animal Health, for final examination. The draft review report was finalised in the meeting of the Standing Committee on 11 March 2011.

The present review report contains the conclusions of the final examination by the Standing Committee. Given the importance of the conclusion of the EFSA, and the comments and clarifications submitted after the conclusion of the EFSA (background document C), these documents are also considered to be part of this review report.

2. Purposes of this review report

This review report, including the background documents and appendices hereto, has been developed and finalised in support of Commission **Directive 2011/44/EU**³ concerning the inclusion of azadirachtin in Annex I to Directive 91/414/EEC, and to assist the Member States in decisions on individual plant protection products containing azadirachtin they have to take in accordance with the provisions of that Directive, and in particular the provisions of article 4(1) and the uniform principles laid down in Annex VI.

This review report provides also for the evaluation required under Section A.2.(b) of the above mentioned uniform principles, as well as under several specific sections of part B of these principles. In these sections it is provided that Member States, in evaluating applications and granting authorisations, shall take into account the information concerning the active substance in Annex II of the directive, submitted for the purpose of inclusion of the active substance in Annex I, as well as the result of the evaluation of those data.

In accordance with the provisions of Article 22 of Regulation (EC) No 33/2008, this review report will be made available for public consultation by any interested parties.

The information in this review report is, at least partly, based on information which is confidential and/or protected under the provisions of Directive 91/414/EEC. It is therefore recommended that this review report would not be accepted to support any registration outside the context of Directive 91/414/EEC, e.g. in third countries, for which the applicant has not demonstrated to have regulatory access to the information on which this review report is based.

² European Food Safety Authority; *Conclusion on the peer review of the pesticide risk assessment of the active substance azadirachtin* EFSA Journal 2010; 8(10):1858. [77 pp.]. doi:10.2903/j.efsa.2010.1858 Available online: www.efsa.europa.eu ..

³ OJ L 100, 14.4.2011, p. 43–46

3. Overall conclusion in the context of Directive 91/414/EEC

The overall conclusion from the evaluation is that it may be expected that plant protection products containing azadirachtin will fulfil the safety requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC. This conclusion is however subject to compliance with the particular requirements in sections 4, 5, 6 and 7 of this report, as well as to the implementation of the provisions of Article 4(1) and the uniform principles laid down in Annex VI of Directive 91/414/EEC, for each azadirachtin containing plant protection product for which Member States will grant or review the authorisation.

Furthermore, these conclusions were reached within the framework of the uses which were proposed and supported by the data submitter and mentioned in the list of uses supported by available data (attached as Appendix II to this review report).

Extension of the use pattern beyond those described above will require an evaluation at Member State level in order to establish whether the proposed extensions of use can satisfy the requirements of Article 4(1) and of the uniform principles laid down in Annex VI of Directive 91/414/EEC.

The following reference values **for the azadirachtin extracts** have been finalised as part of this re-evaluation:

ADI	0.1 mg/kg bw/day
ARfD	0.75 mg/kg bw
AOEL	0.1 mg/kg bw/day

A risk assessment for consumer based on the reference values for the extracts is not possible yet. But in consideration of the “lead compound concept” unacceptable risks for consumer can be excluded. The RMS reported in the Additional Report of December 2009 a long and short-term dietary risk assessment for the lead compound azadirachtin A and indicates a utilisation of <1% of the ADI and of the ARfD for azadirachtin A.

The review has identified several acceptable exposure scenarios for operators, workers and bystanders, which require however to be confirmed for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles.

The review has also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC.

4. Identity

The main identity of azadirachtin is given in Appendix I.

The active substance shall comply with the minimum purity set as Azadirachtin A (see appendix I) At the time of the evaluation a FAO specification was allocated for one of the sources examined.

The review has established that for the active substance notified the aflatoxins are relevant impurities and a maximum limit has been set for their sum (see appendix I).

5. Endpoints and related information

In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 4(1) of Directive 91/414/EEC and the uniform principles laid down in Annex VI of that Directive, the most important endpoints were identified during the re-evaluation process. These endpoints are listed in the conclusion of the EFSA, and at section 3 of this report.

6. Particular conditions to be taken into account on short term basis by Member States in relation to the granting of authorisations of plant protection products containing azadirachtin

On the basis of the proposed and supported uses (as listed in Appendix II), the following particular issues have been identified as requiring particular and short term attention from all Member States, in the framework of any authorisations to be granted:

Member States should pay particular attention to:

- the dietary exposure of consumers in view of future revisions of Maximum Residue Levels;

- the protection of non target arthropods and aquatic organism. Risk mitigation measures should be applied where appropriate.

7. List of studies to be generated

Further studies were identified which were at this stage considered necessary in relation to the inclusion of azadirachtin in Annex I under the current inclusion conditions.

The concerned Member States shall request the submission of further data 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 confirm specifications of technical material, residue definition and groundwater risk assessment.

They shall ensure that the applicant provides such studies to the Commission at the latest by 31 December 2013.

Some other endpoints may require the generation or submission of additional studies to be submitted to the Member States in order to ensure authorisations for use under certain conditions. The list of studies to be generated, still ongoing or available but not peer reviewed can be found in the relevant part of the EFSA Conclusions.

8. Information on studies with claimed data protection

For information of any interested parties, the rapporteur Member State will keep available a document which gives information about the studies for which the data submitter has claimed data protection and which during the re-evaluation process were considered as essential with a

view to annex I inclusion. This information is only given to facilitate the operation of the provisions of Article 13 of Directive 91/414/EEC in the Member States. It is based on the best information available but it does not prejudice any rights or obligations of Member States or operators with regard to its uses in the implementation of the provisions of Article 13 of the Directive 91/414/EEC and neither does it commit the Commission.

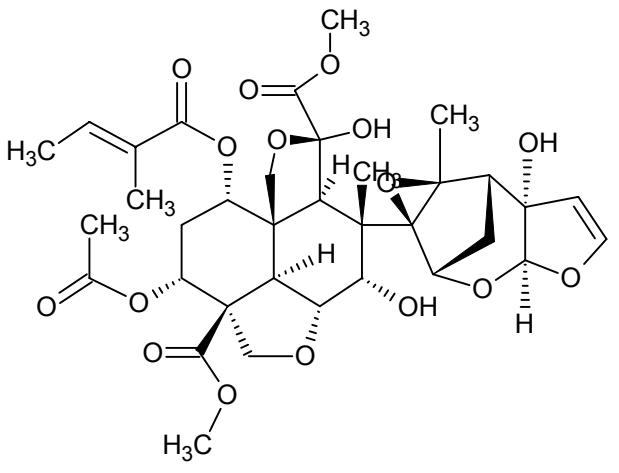
9. Updating of this review report

The information in this report may require to be updated from time to time in order to take account of technical and scientific developments as well as of the results of the examination of any information referred to the Commission in the framework of Articles 7, 10 or 11 of Directive 91/414/EEC. Any such adaptation will be finalised in the Standing Committee on the Food Chain and Animal Health, in connection with any amendment of the inclusion conditions for azadirachtin in Annex I of the Directive.

APPENDIX I

Identity
AZADIRACHTIN

Common name (ISO)	Azadirachtin A (no ISO common name allocated).
Chemical name (IUPAC)	Azadirachtin A: dimethyl (2 <i>aR</i> ,3 <i>S</i> ,4 <i>S</i> ,4 <i>aR</i> ,5 <i>S</i> ,7 <i>aS</i> ,8 <i>S</i> ,10 <i>R</i> ,10 <i>aS</i> ,10 <i>bR</i>)-10-acetoxy-3,5-dihydroxy-4-[(1 <i>aR</i> ,2 <i>S</i> ,3 <i>aS</i> ,6 <i>aS</i> ,7 <i>S</i> ,7 <i>aS</i>)-6 <i>a</i> -hydroxy-7 <i>a</i> -methyl-3 <i>a</i> ,6 <i>a</i> ,7,7 <i>a</i> -tetrahydro-2,7-methanofuro[2,3- <i>b</i>]oxireno[<i>e</i>]oxepin-1 <i>a</i> (2 <i>H</i>)-yl]-4-methyl-8-[[<i>(2E)</i> -2-methylbut-2-enoyl]oxy]octahydro-1 <i>H</i> -naphtho[1,8 <i>a-c</i> :4,5- <i>b'</i> <i>c'</i>]difuran-5,10 <i>a</i> (8 <i>H</i>)-dicarboxylate.
Chemical name (CA)	Azadirachtin A: dimethyl (2 <i>aR</i> ,3 <i>S</i> ,4 <i>S</i> ,4 <i>aR</i> ,5 <i>S</i> ,7 <i>aS</i> ,8 <i>S</i> ,10 <i>R</i> ,10 <i>aS</i> ,10 <i>bR</i>)-10-(acetyloxy)octahydro-3,5-dihydroxy-4-methyl-8-[[<i>(2E)</i> -2-methyl-1-oxo-2-butenyl]oxy]-4-[(1 <i>aR</i> ,2 <i>S</i> ,3 <i>aS</i> ,6 <i>aS</i> ,7 <i>S</i> ,7 <i>aS</i>)-3 <i>a</i> ,6 <i>a</i> ,7,7 <i>a</i> -tetrahydro-6 <i>a</i> -hydroxy-7 <i>a</i> -methyl-2,7-methanofuro[2,3- <i>b</i>]oxireno[<i>e</i>]oxepin-1 <i>a</i> (2 <i>H</i>)-yl]-1 <i>H</i> ,7 <i>H</i> -naphtho[1,8- <i>bc</i> :4,4 <i>a-c'</i>]difuran-5,10 <i>a</i> (8 <i>H</i>)-dicarboxylate
CIPAC No	Azadirachtin A: 627
CAS No	Azadirachtin A: 11141-17-6
EEC No	Not available
FAO SPECIFICATION	627/TK (May 2006) above 250 g/kg up to 500 g/kg ± 15 % of the declared azadirachtin A content. aflatoxins (sum of aflatoxins B ₁ , B ₂ , G ₁ and G ₂) max 0.00003 % of the azadirachtin A content. The specification is related to Trifolio-M and EID Parry.
Minimum purity	111 g/kg azadirachtin A
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern)	Sum of aflatoxin B ₁ , B ₂ , G ₁ , G ₂ = 300 µg/kg azadirachtin A (TC)
Molecular formula	Azadirachtin A: C ₃₅ H ₄₄ O ₁₆

Molecular mass	Azadirachtin A: 720.7 g/mol
Structural formula	 <p>(azadirachtin A)</p>

APPENDIX II
List of uses supported by available data
AZADIRACHTIN

Crop and/or situation	Member State or Country	Product name	F G or I	Pests or Group of pests controlled	Formulation		Application				Application rate per treatment			PHI (days)	Remarks:
					Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Northern Europe Potato	Germany (Northern Europe)	NeemAzal-T/S	F	Colorado beetle	EC	10	Spray	During the vegetation period (irrespective of growth stage)	1	-	0.0042-0.0083	300-600	0.025	4	Treatment at beginning infestation: 5 days after hatching of young larvae
Northern Europe Potato		Oikos	F	Colorado beetle	EC	26	Spray	During the vegetation period (independent from growth stage)	1	-	0.0042-0.0083	300-600	0.025	4	Treatment at beginning of infestation (ca. 5 days after hatching of young larvae)

*as refers to the compound azadirachtin A

<p>(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)</p> <p>(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)</p> <p>(c) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds</p> <p>(d) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)</p> <p>(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989</p> <p>(f) All abbreviations used must be explained</p> <p>(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench</p> <p>(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated</p>	<p>(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypr). In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthialvalicarb-isopropyl).</p> <p>(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application</p> <p>(k) Indicate the minimum and maximum number of application possible under practical conditions of use</p> <p>(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha)</p> <p>(m) PHI - minimum pre-harvest interval</p>
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