COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Substance name: Margosa, ext.; [margosa extract from the kernels of Azadirachta indica extracted with water and further processed with organic solvents]
CAS number: 84696-25-3
EC number: 283-644-7

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
02.12.2014	United Kingdom	Fargro Ltd	BehalfOfAnOrganisation	1
Comment received				
As a supplier of plant protection products we strongly support regulation that is appropriate and based on sound science. There is an issue with a regulation system that is designed to deal with single well defined substances when it comes to botanical extracts, which are a mixture of substances. We support the view that botanical extracts should be regarded as a substance of unknown or variable composition (UVCB). Our particular concern is the biological extract Azadirachtin as registered in the biopesticide NeemAzal®-T/S. The same extract of Neem is classified as a UVCB under the biocide process but as a well-defined substance under the plant protection process. The EFSA peer review established different end points for the different extracts, whereas the CLH report classifies all extracts with the worst of the end points. This leads to confusion and needs to be revised and clarified. NeemAzal®-T/S is an important plant protection product, in both organic and conventional agriculture.				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2014	United Kingdom		Individual	2
Comment received				
I am a formulator of products that use margosa extract, CAS 84696-25-3, and have a vested interest in avoiding the reprotox classification proposed, since I use the margosa extract supplied by Terra Nostra GmbH, and consider that this is a different material to the margosa extract defined above; the Terra Nostra margosa extract is in which the extract is obtained using carbon dioxide in a supercritical state as an extraction agent. It contains a much lower concentration of azadirachtin than the margosa extract extracted with water and further processed with organic solvents. I am keen that these two products be differentiated, so that they do not share the same CLH classification. Should the classification be deemed appropriate for both margosa extracts I can foresee it creating problems for consumer products that use the 'lower azadirachtin' margosa extract, since the appearance of the H361d warning "May cause damage to the unborn child" on the product label would be disproportionate and would deter potential end users from purchasing such products.				

Date	Country	Organisation	Type of Organisation	Comment

				number
05.12.2014	France		BehalfOfAnOrganisation	3
Comment received				
It is hard to apply a regulation scheme, that usually deals with single substances, to extracts of natural origin and to define these mixtures as "active ingredient" (a.i.). "Margosa extract", is the common name for different neem-extracts, available on the market. These different extracts have been gathered in a Taskforce to simplify the approval process. Trifolio-M (our supplier for margosa extract) with its neem seed-kernel-extract called "NeemAzal technical" was one of the notifiers for the inclusion on Annex I to the Directive 98/8/EC. "Margosa extract" was one of the very first botanicals approved and listed on this Annex, and maybe, to some extent, it has paved the path. In the very beginning, during the procedure of approval as a.i., "Azadirachtin" (and so "Margosa Extract", the two terms are used as synonyms in CLH report) was described via the lead component Azadirachtin A. This leads to confusion on the endpoints of the different studies. Quite often endpoints are calculated and expressed as Azadirachtin A while the correct values should refer to the active ingredient "azadirachtin" / "margosa extract". During the process of the peer review for "Azadirachtin" (and so "Margosa Extract") by EFSA different endpoints were established for the different extracts. However, within the CLH-report this is neglected and only one endpoint – the worse of the extracts of the taskforce – is used, leading to the same classification for all extracts. Whereas the use of specific endpoints for each extract would lead to different classifications, as it has already been proposed by EFSA in the "Conclusion of the peer review", in particular in the case of aquatic toxicity.				

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	France		MemberState	4
Comment received				
MS-FR agrees with the classification proposed for Human Health Hazards. We are wondering why Azadirachtin is not classified as Repr.2 H361f. Please argue it. MS-FR agrees with the proposition of classification for Environmental hazards: H410 with a M-factor of 10. Specific comments are required in the specific comments section.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2014	Italy	Terra Nostra Registration Service srl.	BehalfOfAnOrganisation	5
Comment received				
Ladies and gentlemen, in the present list two Margosa extracts are listed in pt 18 and pt 19 under CAS no. 84696-25-3. The supplier and participants are Trifolio GmbH and our company Terra Nostra srl. and Terra Nostra GmbH. The Margosa extr. of Trifolio is an extract from the kernels of Azadirachta indica extracted with water and further processed with organic solvents. Our Margosa extr. is a Co2 extract from the oil of cold pressed neem seeds (Azadirachta indica) without shell. The physico-chemical, toxicological and ecotoxicological properties of The Terra Nostra Margosa extract do not fulfil the criteria for a classification. No labelling is required. Only the safety phrase „Keep out of the reach of children" must be considered. The toxicological studies are part of our dossier. The responsible authority is BauA in Germany. That´s why we note a problem of confusion of dates between the Margosa Extract produced by Trifolio and Terra Nostra. Our customers are completely confused about the present				

situation.
The CAS no. 84696-25-3 describes an unspecified extract which is obtained from constituents of the Neem Tree with an unspecified extracting agent.
The CAS no. 84696-25-3 does not describe a specific substance, but the origin and production process of an undefined mixture of substances or isolated and enriched constituents of the Neem Tree.
Any Margosa extract can be produced e.g. by an extraction with alcohol, by an extraction with chlorinated hydrocarbon or by Co2 extraction. The source can be seeds, the oil, the leaves or bark of the neem tree. It is always an extraction of constituents of the Neem tree.
The various extracts will differ further on: e.g. a cleaned or uncleaned selective extract of one constituent or a cleaned or uncleaned total extract from leaves or seeds.
These differences also relating the physico-chemical properties, the toxicological properties, the effects on target insects and aspired applications.
This is the reason why the characteristics and the classification of the Margosa extract, produced by the german company Trifolio and our Margosa extract is completely different.
Therefore we ask for a possibility to differentiate these both pt 18 and pt 19 Margosa extract´s under CAS no. 84696-25-3 in the present lists/publications.

Details of Terra Nostra srl. and Terra Nostra GmbH Margosa extract:
Substance Name: Margosa, ext. (Co2 Extract from the oil of cold pressed neem seeds (Azadirachta indica) without shell)
EC Number: 283-644-7
CAS Number: 84696-25-3
Dossier submitter: Germany
Proposed classification:
Physical hazards: none
Health hazards: none
Environmental hazards: none

Please contact us if you have any questions.

Best regards,

Franz Schmidt

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TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
02.12.2014	United Kingdom	Fargro Ltd	BehalfOfAnOrganisation	6

Comment received

Whilst supporting regulation it must be based on sound science and representative of actual use. The use of extremely high dose (1,000 mg/kg bw/day) is a level that would never be reached in practical conditions by the use of NeemAzal®-T/S as a plant protection product.

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2014	Germany	GAB Consulting GmbH (on behalf of Trifolio-M GmbH)	BehalfOfAnOrganisation	7

Comment received

In the CLH report, a classification as developmental toxicant (Repr. 2; H361d) was proposed mainly based on the finding of visceral malformations, namely the incidences of ventricular septal defects (VSD), in a teratogenicity study in the rat. However, these incidences of VSD are rather common observation in rats and were very close to historical control data for the laboratory and well within the published historical control data of MARTA (1996). The treatment also caused maternal toxicity in the dams, at both the mid-dose and high-dose group, noted as reduced body weight gain. Although this effect was only transient, it occurred around days 6 to 8 of pregnancy, which has been identified as critical time in the development of the foetal heart. It is, therefore, reasonable to assume that the observed low incidence of VSD is a high dose effect secondary to maternal toxicity rather than a direct effect of Margosa Extract.
Furthermore, no indications of adverse effects on the developing heart were noted in a 2-generation study, in another teratogenicity study in rats, in a teratogenicity study in rabbits, and in several supplemental reports performed with NeemAzal (Margosa Extract) or two other sources of Azadirachtin which were considered toxicologically equivalent in the PPP review of Azadirachtin. Furthermore, published data on developmental toxicity studies also showed no indication of adverse effects. All these data are summarised in the CLH report. Based on the experimental evidence it is appropriate not to classify Margosa Extract with regard to reproductive toxicity. Please refer to the additional statement Pfau (2014): Azadirachtin: Evaluation of Classification and Labelling Proposal with regard to Developmental Toxicity, report no. 234379-A2-050601-01.

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2014	United Kingdom		Individual	8

Comment received

The margosa extract extracted with water and further processed with organic solvents tends to hold circa 4% w/w azadirachtin as an active ingredient. By contrast the margosa extract supplied by Terra Nostra, and subject to CO2 extaction, holds a much lower content of azadirachtin; typically in the order of 0.25% w/w. It is generally accepted that the key mammalian toxin in margosa extract is azadirachtin. Given that the studies where reproductive toxicity was determined required doses that elicited frank toxicity in the dam (refer CLH document, available at:
http://www.echa.europa.eu/documents/10162/3b3e5025-a1f0-4dca-9cc8-b174a5f1fc4d it would be most unlikely that any such signs of reproductive toxicity would be repeated using the Terra Nostra margosa extract in the same experimental models. On this basis it is proposed that the H361d CLH classification is not appropriate for the Terra Nostra margosa extract. Further, to avoid confusion, it is suggested that the Terra Nostra margosa extract be issued with a different EC / CAS number.

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	France		BehalfOfAnOrganisation	9
Comment received				
A detailed statement on the eligibility of classification with Reprotox H 361d concerning the incidences of ventricular septal defects (VSD) has been prepared by the toxicological expert of the taskforce consultant. In addition, we have to keep in mind that in the reproduction studies the test animals were fed with very high dosages of active ingredient (highest dosage 1000 mg/kg bw/day). If we consider the end-use of the product, it should be pointed out that an exposition of 1000 mg a.i./kg bw/day will never be reached under practical conditions. The whole discussion is caused by the fact that "Azadirachtin" is a borderline case with ambiguous findings. The reprotox classification of the product is threatening our product "Proneem" designed for the treatment of the textiles.				

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	France		MemberState	10
Comment received				
P26: part 4.7.1.1 P44: part 4.10.2.2 Please argue the non-classification of Azadirachtin as Repr.2 H361f, considering findings with respect to fertility described for humans in open literature (spermicidal effects in vitro, intravaginal/-uterine used contraceptive) and effects on male and female sexual organs observed in subacute and subchronic toxicity studies in rats (changes in ovary weight, decreased number of corpora lutea, endometrial atrophy in uterus, marked atrophy in testes seminiferous tubular), taking into account that no further mechanistic studies have been submitted to definitively rule out an effect of the active substance on the reproductive system.				

Date	Country	Organisation	Type of Organisation	Comment number
02.12.2014	Germany	Trifolio-M GmbH	BehalfOfAnOrganisation	11
Comment received				
Subject: Setting of specific concentration limits for toxicity for reproduction, referring to Section 4.10 of the CLH report We, Trifolio-M GmbH are to all intents and purposes convinced that a classification with Repr.2; H361d is not appropriate. Independently of our judgement, we acknowledge that the Authorities might come to another conclusion. However, in the case of classification with Repr. 2; H361d, we think specific concentration limits (SCL) above the generic concentration limits (GCL) regarding reproduction toxicity have to be set for Margosa, ext. via the CLH procedure. We want to refer on the recommendation noted in the Guidance on the Application of the CLP Criteria (2013): "According to CLP article 10, (…). SCLs above the GCL may be set where adequate and reliable scientific information shows that the hazard of a substance is not evident at a concentration above the GCLs. Normally substances that fulfil the criteria for reproductive				

toxicity are subject to a harmonised classification an labelling and included in Annex VI to CLP. In such cases, SCLs are set via the procedure for harmonisation of classification and labelling of substances in line with CLP Article 37."(1)
The setting of SCLs is based on the determination of an ED10. According to the guidance document "for effects that are measured as changes in incidence, such as an increase in the number of malformations or resorptions, the ED10 is defined as the dose level at which 10% of the test population above the incidence in the concurrent control shows the effect."(2)
When taking the data of the relevant study (Myers & Dawe, 1997; CLH-report p.40-42) into account, Margosa, ext. has to be regarded as a borderline case with low incidences of critical observations and a high dosage of the test substance (up to 1000 mg/kg bw/day). In this study, even the values of the highest dose group did not exceed the ED10 level, neither concerning percentage malformation per foetuses, nor percentage per litters. Theoretically an ED10 >1000 mg/kg bw/day would have been calculated.
Substances which are classified in Category 2 for reproductive toxicity with an ED10 >400 mg/kg bw/day can be placed in potency group 3 (low potency) leading to SCLs above 3%.

Therefore, in the case that Repr. 2 H361d will be committed in the final conclusion of the CLH procedure, we claim to associate Margosa, ext. with the low potency group 3, referring to an ED10 ≥400 mg/kg bw/day.(3)

Footnotes:
(1) Guidance on the Application of the CLP Criteria, Version 4.0 – November 2013, Annex VI: Background Document to the Guidance for Setting Specific Concentration Limits for Substances Classified for Reproductive Toxicity According to Regulation (EC) No 1272/2008, p. 646
(2) Guidance on the Application of the CLP Criteria, Version 4.0 – November 2013, p. 424
(3) Guidance on the Application of the CLP Criteria, Version 4.0 – November 2013, p. 430

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2014	Germany	GAB Consulting GmbH (on behalf of Trifolio-M GmbH)	BehalfOfAnOrganisation	12

Comment received

In the CLH report, toxicological data is presented for three sources of Azadirachtin, which were found to be toxicologically equivalent during the PPP EU review of Azadirachtin. Only one of them, named NeemAzal, fully corresponds to the substance identity information given in Part B point 1.1 of the CLH report on Margosa Extract.
A classification as Skin Sensitising Category 1 (without sub categories) is proposed in the CLH report since study results for two tested extracts led to the classification 1B, while one study led to classification 1A.
It is proposed that classification as 1B is sufficient given that the test for NeemAzal (the only extract which is identical to Margosa Extract) led to a classification 1B. Furthermore, a sensitisation study with the formulated product also did not show any sensitising effects. Please refer to the additional statement Pfau (2014): Margosa Extract: Evaluation of Classification and Labelling Proposal with regard to Skin Sensitisation, report no. 126243-A2-050206-01.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2014	Germany	GAB Consulting GmbH (on behalf of Trifolio-M GmbH)	BehalfOfAnOrganisation	13

Comment received

Acute aquatic toxicity:
Please note that the acute endpoint for fish 96h-LC50 = 4.14 mg a.s./L mentioned in Part B, Point 5.4 (Table 43) and Point 5.4.1 (Table 44) on page 59 is incorrect. The study was performed with the product NeemAzal-T/S. In the assessment report (AR) an endpoint of 141 mg NeemAzal-T/S /L was derived. Since the NeemAzal-T/S used in this study contained 4 % Margosa extract, the correct 96h-LC50 is 5.6 mg Margosa extract/L. (In the AR a content of 3% was used for this calculation.)
We agree with the conclusion that no classification for acute aquatic toxicity is required.

Chronic aquatic toxicity:
The proposal for chronic classification (see Part A, page 6, Table 2, page 8 Table 3, Part B, Point 5.6, page 66) is based on a NOEC of 6 µg/L derived from a study with the sediment dwelling midge Chironomus riparius (see Part B, Point 5.4.4 and 5.5, page 64ff). Due to the rapid disappearance of Azadirachtin A in the water-sediment system of this study, this concentration for the no-observed effect level was calculated in the CLH report with the following construct:
"the mean of the NOEC based on nominal concentrations and the ½ LOQ (for water and pore water, because no test substance was found in the sediment) was calculated" (see Part B, Point 5.4.4, page 64 of the CLH report). This approach was also used in the PPP evaluation of Azadirachtin under Council Directive 91/414 EEC. However, we consider such interpretation of the study scientifically unjustified:
The effects of NeemAzal (i.e. Margosa Extract) and NeemAzal-T/S on Chironomus riparius were investigated experimentally (Gonsior 2008a and 2008b, report No. 2007/1356/01-ASCr and 2007/1355/01-ASCr, summarised in Part B, Point 5.4.4 of the CLH report).
In these studies the test items were applied into the water column. The concentrations in water just after application were 86.7% and 75.5% of the nominal values, respectively, for NeemAzal and NeemAzal-T/S, in the treatment groups corresponding to the NOEC value. In the study with NeemAzal, further 9.2% of the applied test item was found at test start in the pore water of the treatment group corresponding to the NOEC, while no further test item was found in the pore water at the test start in the study with NeemAzal-T/S.
Seven and 28 days after test start the concentrations were below the limit of detection in all three compartments.
In the studies, the endpoints were calculated based on the concentrations at test start: In the study with NeemAzal the test endpoints were calculated based on the nominal concentration since concentrations at test start were > 80%. In the study with NeemAzal-T/S the endpoints were calculated based on the nominal and in addition based on the actual concentration at test start (since concentrations at test start were < 80%).
In contrast to this the endpoints in the CLH report have been calculated based on the time-weighted average concentration. However, in contrast to the other aquatic studies in which organisms are exposed via water only, this approach is not comprehensible for studies with Chironomus riparius. The OECD 219, paragraph 43 recommends: "Effects concentrations expressed as concentrations in the overlying water, are calculated preferably based on measured concentrations at the beginning of the test".
The analytics in this test system primarily serve the confirmation of the nominal test concentration at start of the study in order to exclude mistakes in the application. In a multi-compartment system, it is not expected that concentrations are stable in each compartment. Therefore, exposure of the test organisms is complex and occurs via water,

porewater, sediment and via diet. The share of the individual compartments on the overall exposure cannot be distinguished. Thus, the relevance of the course of concentrations in the individual compartments for the overall result of the study is not clear.
In the chronic studies with Chironomus riparius the larvae are exposed during
a) the development in the sediment,
b) the consumption of feed on the sediment surface and finally
c) the pupation in the water column and
d) hatch in the water surface.
During the whole test period interactions may occur between the test item, the compartments and the test organisms which are similar to those which may occur under natural conditions. These interactions are wanted in the same way as they are wanted e.g. in mesocosm studies, in which additionally interactions with other organisms and a more rapid degradation by weathering is possible to occur. In our opinion it is appropriate to base the study endpoints on the initially measured test concentrations as requested by OECD 219.
The NOEC for NeemAzal (i.e. Margosa Extract) is 18.4 µg NeemAzal/L, based on nominal concentrations.
The NOEC for the product NeemAzal-T/S is 13.0 µg NeemAzal/L, based on initially measured concentrations.
Thus the most critical and therefore relevant endpoint for the classification of Margosa Extract is the NOEC of 13.0 µg NeemAzal/L.
The corresponding classification would therefore be Aquatic Chronic 1; H410 with M-factor 1, if it was concluded that the Margosa Extract is not degradable (see below for a justification for degradability). Please also note that Chironomus riparius is neither a fish, crustacea, algae, or other aquatic plant and therefore does not fall into the groups of test species mentioned in Regulation (EC) No 1272/2008 for classification regarding chronic effects.

(Please note that the chronic endpoint for fish NOEC = 1.9 mg a.s./L mentioned in Part B, Point 5.4.1.2 (Table 45) on page 60 is incorrect. The study was performed with the product NeemAzal-T/S. In the Additional Report to the DAR (AR) an endpoint of 63.6 mg NeemAzal-T/S /L was derived. Since the NeemAzal-T/S used in this study contained 4 % Margosa Extract, the correct NOEC is 2.5 mg Margosa Extract/L. (In the AR a content of 3% was used for this calculation.)
Similarly, the chronic endpoint for Daphnia NOEC = 0.1 mg a.s./L mentioned in Part B, Point 5.4.2.2 (Table 47) on page 62 is incorrect. The study was performed with the product NeemAzal-T/S. In the Additional Report (AR) an endpoint of 3.4 mg NeemAzal-T/S /L was derived. Since the NeemAzal-T/S used in this study contained 4 % Margosa Extract, the correct NOEC is 0.14 mg Margosa Extract/L. (In the AR a content of 3% was used for this calculation.))

Degradability:
In the CLH report it was concluded from standard screening tests that Margosa Extract is not readily biodegradable. It was also found in these studies that Margosa Extract is not inhibitory.
However, based on the further evidence presented below, it is shown that the leading compound Azadirachtin A exhibits rapid degradability and, hence, the classification and labelling of Margosa Extract have to be reconsidered.

It is true that Regulation (EC) No 1272/2008 mentions biodegradation screening tests (see Point 4.1.2.9.2. of Annex I) as "one way of demonstrating rapid degradation", but also states that "a fail in the screening test does not necessarily mean that the substance will not degrade". It "allows the use of data to show that the substance did actually degrade

biotically or abiotically in the aquatic environment by > 70 % in 28 days. Thus, if degradation is demonstrated under environmentally realistic conditions, then the criterion of 'rapid degradability' is met." Under Point 4.1.2.9.3 of Annex I it is also stated that "primary biodegradation does not normally suffice in the assessment of rapid degradability unless it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment."

As shown in the CLH report Azadirachtin A in water is mainly subject to base-catalysed hydrolysis. Also indirect photolysis and microbial degradation are expected to contribute significantly to the degradation of Azadirachtin A or Margosa Extract, resp., in natural water bodies under conditions of use.
However, simulation tests and relevant literature data were not considered for classification and labelling purposes although available.
As presented in the CLH report for Azadirachtin, a rapid disappearance of Azadirachtin A was confirmed in a water metabolism study by Molinari (2002), resulting in a DT50 value in water of 13.7 days (20 °C), clearly below the trigger value of 16 days. Since a follow-up of degradation products is not possible due to the limitations in radio-labelling and substance synthesis (see also Point 5.1.2.3 of CLH report for Margosa Extract), information on degradation products could not be derived from this study. First evidence is available from the biodegradation screening tests, confirming no relevant inhibition of microbial activity in STP effluent.
Detailed information is available from the following studies, all part of the Annex I inclusion procedure of Azadirachtin (PPP):
In order to characterise the degradation products of Margosa Extract with regard to their ecotoxicological potential, fish and aquatic invertebrates were exposed to aged NeemAzal (identical with Margosa Extract) residues in water (Teigeler, 2009; Simon, 2009).
NeemAzal was applied into the water phases of two water-sediment systems of different trophic conditions to give a final concentration of 45 mg NeemAzal/L, corresponding to 13.8 mg Azadirachtin A/L, a concentration at which effects on fish and aquatic invertebrates could be expected. Water samples were taken 1 hour, and on day 3, day 7, day 14 and day 21 after treatment for chemical analysis (Geschke, 2009) and for the exposure of test animals.
In the subsequent bioassays fish (Oncorhynchus mykiss) and water fleas (Daphnia magna) were exposed to these (undiluted or diluted) water samples to determine the effects of NeemAzal water residues.
In the study on fish, neither in the first bioassay with Oncorhynchus mykiss performed one hour after application of NeemAzal to the water-sediment system, nor in consecutive bioassays with water samples containing degradation products of NeemAzal, effects on fish were observed up to the highest test rate.
In the study on Daphnia magna, a clear dilution-response relation was observed for both water sources in the first two bioassays performed with water samples taken 1 hour or 3 days after application, resp. The EC50 values were determined to be 11.3 and 11.4 mg initial NeemAzal/L for 1-hour water samples of the clayey silt water-sediment system and sandy water-sediment, respectively. For 3-days water samples the EC50 values were determined to be 28.7 and 31.7 mg initial NeemAzal/L for the clayey silt and sandy water-sediment systems, respectively. In the following bioassays the EC50 values were > 45 mg initial NeemAzal/L for aged water samples from both sediment-water systems.
The decline of effects was thus correlated to the decline of Azadirachtin A in the water samples confirming that degradation products of Margosa Extract in water are significantly less toxic than the unaltered Margosa Extract.
Further details can be found in the statement by Otto & Häusler (2009): Statement on the relevance of degradation products of Azadirachtin in aquatic systems, report no. 234379-A3-0708-02, attached to this submission.
Hence, the criteria for rapid degradability – fast removal from the environment and non-

hazardousness of degradation products – are met by Margosa Extract.
Further evidence is based on the bioaccumulation potential and LogPow of Azadirachtin A which are significantly below the trigger value as fixed in Regulation (EC) No 1272/2008.
Thus, as Margosa Extract is rapidly degradable and the lowest NOEC is > 0.01 mg/kg, the corresponding classification should therefore be Aquatic Chronic 2; H411.

Date	Country	Organisation	Type of Organisation	Comment number
02.12.2014	United Kingdom	Fargro Ltd	BehalfOfAnOrganisation	14
Comment received				
Use of Chironomus is not relevant for the classification of chronic toxicity when evaluating NeemAzal® technical. CLP-regulation (EC) No. 1272/2008 amended by regulation (EU) No. 286/2011 (Annex I 4.1.2.7)1 concerning tests of species other than fish, crustacae and algae says that only in the classification of acute toxicity should other species be used for the classification. For the chronic toxicity only the NOEC´s (or EC10-values) of fish, crustacae and algae should be used for classification. Moreover, due to the slow mode of action of NeemAzal® technical the species Chironomus is inappropriate for the assessment of a long-term toxicity. Relevant surface water species are already considered by mitigation measures e.g. buffer zones.				

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	France		BehalfOfAnOrganisation	15
Comment received				
Use of Chironomus studies for classification: Results of studies with the midge Chironomus riparius have been used to set the NOEC relevant for the classification of aquatic chronic toxicity. We hold the opinion that Chironomus riparius is not an organism relevant for classification of chronic toxicity. The respective passages in the CLP-regulation (EC) No. 1272/2008 amended by regulation (EU) No. 286/2011 (Annex I 4.1.2.7)1 concerning tests of other species than fish, crustacae and algae reveal that only in the classification of acute toxicity other species than fish, crustacae or algae can be used for the classification. For the chronic toxicity only the NOEC´s (or EC10-values) of fish, crustacae and algae should be used for classification. Chironomus studies as best suited non-target test organism for the classification of the aquatic toxicity of insecticides is questioned generally. Recalculation of NOEC: The poor recovery rates in the studies with Chironomus riparius (below the limit of quantification- LOQ), have led to a recalculation of the study-endpoints during the approval-process of the active substance: the actual amounts measured were not accepted to establish the NOEC. Instead, the geometric mean values were calculated by using the study endpoint and the LOQ. It is not comprehensible, why an endpoint which was determined in a study done under GLP and by using OECD guidelines is not accepted and has to be changed although the respective studies were accepted and considered valid. It leads, in consequence, to the presumption that the higher the LOQ the higher is the NOEC.				

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	France		MemberState	16
Comment received				
- First, few comments in order to help the document reading:				

-Section 5: Could you please add few explanations about the use of Azadirachtin A as margosa representative?
-Section 5.1 Could you precise if degradation test are based on margosa extract or on Azadirachtin A in table 34
-Table 43: could you please precise on which substance the test was done? Same remark for table 46
-Section Long term invertebrate toxicity: could you precise how was measured the test substance? By using azadirachtin A as lead substance?
-Section 5.4.4. In the description of the text could you precise each time which substance is measured?
- Then classification analysis
MS-FR agrees with the proposition of classification: H410 with a M-factor of 10.

Date	Country	Organisation	Type of Organisation	Comment number
02.12.2014	Germany	Trifolio-M GmbH	BehalfOfAnOrganisation	17

Comment received

Statement on the classification of the substance Margosa, ext. in the CLH report with respect to Aquatic Toxicity.

In the "CLH report Proposal for Harmonised Classification and Labelling Substance Name: Margosa, ext." the substance Margosa, ext. is classified as Aquatic Chronic, Category 1, H410 with an M-Factor of 10 regarding the risks to the environment (see p. 65/66 CLH report). Trifolio-M does not share this view with respect to the available studies:
Chironomus riparius should not be considered for long-term (chronic) Aquatic Toxicity-classification. According to CLP-regulation (EC) No. 1272/2008 for the aquatic chronic classification only studies with fish, crustacae and algae shall be used. For long-term effects the lowest endpoint of fish, crustacae and algae is the NOEC = 1.84 mg a.s./L from the study with Daphnia magna, which does not trigger a classification.
In order to protect these species, other measures, like buffer zones to natural waters, have been implemented in the product registration by the authorities. These measures were based on aquatic toxicity values that were found to be most critical for Chironomus riparius. With these buffer zones a harmful effect on the midge can be excluded. In the light of the mode of action of Margosa, ext. the long-term studies with Chironomus riparius seem to be irrelevant. It is known that NeemAzal® technical has a slow mode of action to several insects. It does not kill the insects immediately, but influences their development. Therefore, no conclusion concerning long-term toxicity of the corresponding studies could be taken since the test organisms could have been already poisoned from the very beginning.
Trifolio-M does not comprehend in general, why a study endpoint, measured in valid studies that were done according to the respective OECD guideline and under GLP is not accepted. Instead, the evaluators calculated mean values by using the resulting endpoint and the LOQ/2 of the study (p. 64 CLH report) - an approach, which is not comprehensible in the light of the relevant guidelines. Endpoints should be based on nominal or actual test concentrations as requested by OECD 219.
Irrespective of the disagreement of Trifolio-M to the consultation of the Chironomus riparius studies for the long-term aquatic toxicity, if these studies are to be considered, a NOEC of 0,0184 mg a.s./l should be defined.
Please refer to the attached statement (Trifolio 2014): Statement on the classification of the substance Margosa, ext. in the CLH report with respect to Aquatic Toxicity.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	France		MemberState	18
Comment received				
We have a specific comment regarding Part A table 3 (p7): Points 2.1 to 2.16 should be completed in the table 3 even though no classification is necessary in a physical and chemical point of view.				

ATTACHMENTS RECEIVED:

1. **Azadirachtin: Evaluation of Classification and Labelling Proposal with regard to Developmental Toxicity**, report no. 234379-A2-050601-01 (refer to comment 7)
2. **Margosa Extract: Evaluation of Classification and Labelling Proposal with regard to Skin Sensitisation**, report no. 126243-A2-050206-01 (refer to comment 12)
3. **Statement on the relevance of degradation products of Azadirachtin in aquatic systems**, report no. 234379-A3-0708-02 (refer to comment 13)
4. **Statement on the classification of the substance Margosa, ext. in the CLH report with respect to Aquatic Toxicity** (refer to comment 17)