Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Spiroxamine (ISO); 8-tert-butyl-1,4-dioxaspiro[4.5]decan-2-ylmethyl (ethyl)(propyl)amine

EC number: N.A.
CAS number: 118134-30-8

CLH-O-0000001412-86-76/F

Adopted

11 September 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SPIROXAMINE(ISO)

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.
All attachments including confidential documents received during the public consultation have been provided in full to the dossier submitter, to RAC members and to the Commission (after adoption of the RAC opinion). Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website.

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Substance name: Spiroxamine (ISO); 8-tert-butyl-1,4-dioxaspiro[4.5]decan-2-ylmethyl(ethyl)(propyl)amine
EC number: -
CAS number: 118134-30-8
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
20/08/2014	**Germany**	**Bayer CropScience AG**	**Company-Manufacturer**	**1**

Comment received

CLH report
Proposal for Harmonised Classification and Labelling
Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2
Substance Name: Spiroxamine
Version number 2, date 2014-06-23

Comments on Efate and Ecotox

1. Section of the CLH report:
Part B – point 5.1.1.1 –
Hydrolytic degradation
(page 56f)

Information in CLH report for spiroxamine:

The CLH report for SPX states on page 56:
"In the hydrolysis study by Brumhard (1995, refer to RAR: IIA7.5/01) conducted at 25 °C using buffer solutions of pH 5, 7 and 9 spiroxamine showed hardly any degradation over the examined testing period of 30 days. At termination of the experiment spiroxamine (KWG 4168) was accounted for 97.3 - 99.5 % of the radioactivity recovered in the solutions."

The CLH report for SPX states on page 56:
"As a result, small amounts of three metabolites were detected (max. 4 %) which in their behavior corresponded to the reference compounds N-oxide (M03), despropyl (M02) and desethyl (M01). ."

BCS comment to point 1.:

The original report by Brumhard (1995) states:
"KWG 4168 was stable at pH 5 and 7. Under the experimental conditions formation of hydrolysis products was observed only in one of the two experiments at pH 9, respectively. All degradates

yielded far below 10 % of the applied radioactivity at any time during the study. At termination of the experiment KWG 41 68 was accounted for 90.7 - 99.5 % of the radioactivity recovered in the solutions."

The original report by Brumhard (1995) states:
"The three metabolites were found to be identical with the authentic reference substances.WAK 6301, KWG 4669 and KWG 4557. … The metabolites reached on average of the two vessels a maximum portion of 4.5 % of the applied radioactivity."

2. Section of the CLH report:

Part B – point 5.1.2 – Biodegradation estimation
(page 59f)

Information in CLH report for spiroxamine:

The report states on page 59: "Conclusion:
The results of this test show that spiroxamine (KWG 4168) was degraded in aquatic systems to (DegT50 in the system 28 days and 106 days). …"

BCS comment to point 2. :

The sentence is incomplete as it does not state to what spiroxamine was degraded in aquatic systems. The sentence should read as follows:
"The results of this test show that spiroxamine (KWG 4168) was degraded in aquatic systems to KWG 4168-N-oxide (M03), KWG 4168-acid (M06) and CO2 (DegT50 in the system 28 days and 106 days).

The evaluation of rapid degradability should be based on higher-tier mesocosm studies as environmentally realistic conditions.
According to the DAR Vol.3 B.9.2.1.9 (dated 27 January 2010), "The mean DT50-value for the whole system (water plus macrophytes plus sediment) was 7.22 days" in nine outdoor mesocosm systems (Bruns et al. 2008, document No. M-304557-01-1). Although the DAR states that this value should be considered with caution since the fate of the test substance in the sediment showed a fluctuating pattern, the fluctuating pattern is accounted for by the large number of individual test systems (nine) and by using a mean value. In addition, the value is supported by the results from additional mesocosm systems (DAR vol.3 B.9.2.4; Heimbach et al. 2000, M-030336-01-1): In an enclosure with macrophytes and an organic-rich detritus layer, the DT50 was 10.1 days for the total system. In the two enclosures without macrophytes and without the organic-rich detritus layer, the DT50 value for the total system was 9.6 days. DegT50 for the whole system between 7.22 and 10.1 days means that more than 70 % is degraded in 28 days.
Since the DT50 (whole system) were < 16 days in aerobic water-sediment mesocosm systems it can be concluded that spiroxamine undergoes rapid primary degradation in the environment. In conclusion, spiroxamine is considered to be rapidly degradable in the aquatic environment according to the CLP regulation as it meets the criterion of >70% degradation in 28 days and because the two major metabolites in the water sediment systems (KWG 4168-N-oxide (M03) and KWG 4168-acid (M06) do not fulfil the criteria for classification as hazardous to the aquatic environment (The ErC50 values for the green alga Desmodesmus subspicatus, which is the most sensitive species, are 31.680 mg/L for KWG 4168-N-oxide (M03) and > 3.2 mg/L for KWG 4168-acid (M06)).

3. Section of the CLH report:

Part B – point 5.3.1.2 –
Long-term toxicity to fish
(page 59f)

Information in CLH report for spiroxamine:

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The report states on page 60: "The overall NOEC for the FFLC test was the EC10 for the survival observed in the F1-ELS of 2.0 µg as/L."

BCS comment to point 3.:

The EC10 cannot be equated with the NOEC. The NOEC of the study by Teigeler (2009) is 0.0026 mg as/L. The EC10 was calculated to be 0.002 mg as/L.
It is proposed to re-phrase the sentence as follows: "The overall endpoint for the FFLC test was the EC10 for the survival…."

Dossier Submitter's Response

Thank you for your general comments related to Sections of the CLH report

1) Part B – point 5.1.1.1 –Hydrolytic degradation:
There is no difference in meaning of the CLH report summary of this study and the original report by Brumhard (1995).

2) Part B – point 5.1.2 – Biodegradation estimation:
We do not agree with the stated opinion of BCS related to rapidly degradation of Spiroxamine in the sense of CLP Regulation. The standard tests which are recommended for classification and labelling purposes in the field of evaluation of degradation are quite different then the cited outdoor mesocosm study, which is not run after a standardized protocol and under defined laboratory conditions for evaluation of rapid degradability.
Spiroxamine is not rapidly degradable in the sense of CLP-regulation.

3) Part B – point 5.3.1.2 – Long-term toxicity to fish:
Of course there is a difference in meaning of NOEC (no observed effect concentration as a value of concentration of the substance in a study) and EC10 (statistical calculated effect concentration with 10% effect to the organisms).
The cited wording from CLH report is unfortunately not clear.
The NOEC received in the original FFLC-study report from Teigeler (2009) with zebrafish *Danio rerio* was given with 0.0026 mg/L. However at this lowest tested concentration 35% effect on mortality of F1 generation were observed and therefore an EC10 of 0.002 mg/L was recalculated from the competent authority for evaluation of environmental toxicity of Spiroxamine and used as "surrogate NOEC" for risk assessment purposes.
It is accepted to re-phrase the sentence as follows:
"The overall relevant endpoint ("surrogate NOEC") for the FFLC test was the EC10 for the survival observed in the F1-ELS of 2.0 µg as/L."

RAC's response

The comments on hydrolysis and long-term fish toxicity do not affect the classification proposal. RAC notes that the CLP Guidance (Annex II, Section II.2.3.2) states that data from mesocosm experiments can in principle be used for assessing the potential for rapid degradation, provided that ultimate degradation can be demonstrated. Since no information on ultimate degradation is available from these studies, RAC considers that the results cannot be used for classification. In this case, standard water-sediment simulation studies with two sediment types gave whole system DT_{50}s of 106 days and 28 days (with 7 or 17 per cent mineralisation by the end of the test), respectively. This suggests that there may be some circumstances where degradation is not as rapid as suggested by the mesocosm experiments. On this basis, RAC considers the substance to be not rapidly degradable. In addition, the stakeholder comment only refers to two major metabolites in the mesocosm studies, whereas simulation studies imply the formation of at least four other substances, the hazard classification status of which is unknown.

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Date	Country	Organisation	Type of Organisation	Comment number
13/08/2014	**The Netherlands**		**MSCA**	**2**

Comment received

The Netherlands agrees with the classification Repro. 2 (H316d) made by Federal Institute for Occupational Safety and Health (Germany) but disagrees with some of the arguments provided that lead to the discrimination between category 2 and 1B. Data on repeated dose-toxicity studies would help assess whether the fetal effects are secondary to the maternal toxicity, and data on effects of Spiroxamine on the formation of steroid hormones would provide useful mode of action and human relevance information.

With regards to classification of Skin Sens. 1B, The Netherlands disagrees with this classification because of insufficient data for sub-categorization and suggests keeping the current classification of Skin Sens. 1 (H317).

Other comments:
-pg.4, Section 4: 'Hence only acute toxicity and developmental toxicity endpoints are addressed in this dossier'. Should skin sensitization be added given the assessment in section 4.6.1 on pg. 22-27?
- Pg. 25, the purity of Spiroxamine in the human study was reported to be very low (5.6%,). Is this a typo? Where the concentration corrected for this purity?

Dossier Submitter's Response

Regarding classification Repr. 2 (H316d):
Maternal effects (clinical symptoms) observed in the developmental toxicity study were sufficiently presented in Table 44 for the relevant dams at 100 mg/kg bw/d (NOAEL 30 mg/kg bw/d).
For further information, the NOAEL of a 4 week feeding study in rats was 3.4 mg/kg bw/d (30 ppm) based on increased liver weight, steatosis of hepatocytes, hyperkeratosis of oesophagal mucosa at 10.8 mg/kg bw/d, at 33.6 mg/kg bw/d (300 ppm) additionally liver enzyme induction, hyperplasia of bladder epithelium. In a second 4 week study (gavage) no NOAEL could be established due to clinical signs (salivation, transient tremor, dacryosialosis, digging activities) even at 10 mg/kg bw/d.
Studies on effects on the formation of steroid hormones provoked by Spiroxamine have not been provided.
Regarding classification of Skin Sensitisation:
Noted. Decision is up to ECHA/RAC
Other comments:
Page 13 (not 4): Agreed. The sentence should be revised accordingly: 'Hence only acute toxicity, skin sensitisation and developmental toxicity endpoints are addressed in this dossier…..'.
Page 25: Thanks to the Netherlands, it is a typo. The exact value is 95.6% and should be revised in the CLH Report, accordingly.

RAC's response

Regarding classification as Repr. 2 (H316d):
Thank you for suggesting the arguments to consider in assessing the classification of spiroxamine for developmental toxicity.
Regarding classification for Skin Sensitisation:
RAC is of the opinion that the classification as Skin Sens. 1 (without sub-categorisation) should be retained.

Date	Country	Organisation	Type of Organisation	Comment number
01/08/2014	**Spain**		**MSCA**	**3**

Comment received

The Spanish CA agrees with the spiroxamine classification proposal for the human health, based on the same reasoning than the German CA. Therefore, we supports to classify spiroxamine as: Repr.2 / H361d, Acute Tox. 4 / H332, Acute Tox. 4 / H312, Acute Tox. 4 / H302, Skin Irrit. 2 / H315, Skin Sens.1B / H317 under Regulation (EC) 1272/2008 and as Repr. Cat. 3; R63, Xn; R20/21/22, Xi; R38, R43 under Directive 67/548/EEC.

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Dossier Submitter's Response
Thanks to Spain!
RAC's response
The opinion is noted and supported except for Skin Sens. 1B; RAC is of opinion to not subcategorise in the classification for skin sensitisation.

Date	Country	Organisation	Type of Organisation	Comment number
22/08/2014	**France**		**MSCA**	**4**
Comment received				
FR agrees with the classification proposal for human health hazards and M factors proposed for Environmental hazards.				
Dossier Submitter's Response				
Thanks to France!				
RAC's response				
The opinion is noted and supported.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
22/08/2014	Belgium		MSCA	5
Comment received				
Even if the reproductive toxicity is not part of the CLH proposal, we would like to express some remarks. The palatoschisis observed in 3 foetuses out of 3 litters occurred without adverse maternal toxicity. The only maternal effects observed are a significant decreased of the body weight without clinical signs or symptoms. In the previous range studies, the palatoschisis is observed at the same dose level of maternal toxicity. In the R6072 study (100mg/kw bw/d) , the palatoschisis is observed in 3/46 foetuses in 2 litters. Those effects are observed in the litters where the dams presented clinical symptoms. In the R6355 study (150 mg/kg bw/d), the palatoschisis is observed in 3/18 foetuses where only 4 dams survived (Mortality 21/25) and they presented clinical symptoms (but no information on the severity of the symptoms). It is difficult to establish a causal relationship between reproductive and parental toxicity. If possible, it would be recommended to correlate individual data for offspring and their parents in the main study in rats presented in the dossier. And even if a causal relationship is established, we should keep in mind that the effects in the offspring may still be relevant for developmental classification, dependent on the severity of the effects and a classification Cat.2 can be warranted				
Dossier Submitter's Response				
In the main developmental toxicity study in rats (Becker, H. and K. Biedermann, 1992) no clinical symptoms were reported up to the highest dose of 100 mg/kg bw/d. Only slight signs of maternal toxicity were reported: Decreased food consumption and body weight, and significant decreased body weight gain only after correction for uterus weight. One case of perforating gastric ulcer was observed. The fact, that no clinical symptoms were reported was commented by the notifier as follows:' …that in this study, which was conducted at RCC 1990 over Christmas, the intensity of clinical observations might have been reduced' (Henninger, K. 2009). Based on the available data and information in the study report, dossier submitter cannot comment on the validity and soundness of this argument. However, one may assume, that clinical symptoms occurred at 100 mg/kg bw/d, because even in the acute toxic dose study clinical signs like apathy and increased salivation were reported in 10/10 animals (females and males). In the R6355 study the extreme high maternal mortality (21/25) may forebode the severity of clinical symptoms in the surviving animals, but a detailed description is missing in the study report. For individual clinical symptoms observed in this study please refer to section 7 of the CLH Report.				
RAC's response				
It is agreed that Cat. 2 is warranted				

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Date	Country	Organisation	Type of Organisation	Comment number
13/08/2014	The Netherlands		MSCA	6
Comment received				
Reproductive toxicity Current classification: no classification for reproductive toxicity Proposed: Repro. 2 (H316d) The Netherlands agrees with the classification of Repro 2 (H316) made by Federal Institute for Occupational Safety and Health (Germany). We agree that the only observation of concern for developmental classification is the increase in palatoschisis in the rat. As this increase was above the concurrent and historical controls and the effect was confirmed in the range finding study, this effect is considered to be treatment-related. In our opinion, these effects could result in classification in category 2 or 1B. We agree that the incidence of palatoschisis is low. However, we do not agree that a low incidence of a treatment related effect would affect the classification category. Therefore, we do not agree that the low incidence would argue for category 2. We also do not agree with the argument that because this effect was only observed in rats and not in rabbits justifies classification in category 2 instead of category 1B. In principle, an effect in one species would warrant classification (also in category 1B) unless it is shown that this effect is not relevant to humans. We agree that the presence of maternal toxicity at the dose level at which developmental effects are observed could reduce the concern to category 2. However, this would require an assessment whether the fetal effects are secondary to the maternal toxicity (see paragraph 3.7.2.3.4 of Annex I). This is currently not possible due to the limited information for example on the dose levels that induce toxicity in the repeated dose studies and whether these type of effects could cause the fetal effects as observed in the rat developmental study. Also relevant could be information regarding the effect of Spiroxamine on the formation of steroid hormones as this substance is a fungicide affecting the sterol synthesis in fungi. Some other fungicides that also affect sterol synthesis affect steroidogenesis in mammals resulting also in increases in cleft palate.				
Dossier Submitter's Response				
Noted, please refer to DSR on Comment 2				
RAC's response				
Thank you for suggesting the arguments to consider in assessing the classification of spiroxamine for developmental toxicity.				

OTHER HAZARDS AND ENDPOINTS – Acute toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22/08/2014	Belgium		MSCA	7
Comment received				
We support the DS for the classification Acute Tox.4 , H302-H312-H332. The results from the studies presented in the dossier are within the range of the new CLP-classification criteria				
Dossier Submitter's Response				
Thanks to Belgium!				
RAC's response				
The opinion is noted and supported.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation

Date	Country	Organisation	Type of Organisation	Comment number

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22/08/2014	Belgium		MSCA	8

Comment received

We also support the classification skin sensitisation category 1B. The Guinea pig maximisation test and the blueher test indicate results fulfilling the CLP criteria for subcategorisation 1B. However we would recommend the DS to check the table 18 (Number of animals exhibiting skin reactions in the maximisation test) as it appears that there is some inconsistency between the text and the table (p23 "After the 1st challenge, 14 out of 20 test group animals responded to the 1% test article formulation…." But in the table, only 11 animals reacted at the 1st challenge at 1%).
Another recommendation would be to evaluate the potency of Spiroxamine based on the scoring established in the table 3.4.2-e in the CLP criteria Guidance.

Dossier Submitter's Response

All in all, 14 out of 20 test group animals responded to the 1% test article formulation: 11 animals after 48 hours and additionally 3 animals only after 72 hours (as mentioned below table 18 of the CLH report). Furthermore, 4 out of those 11 animals (48 hours) were non-responder at 72 hours. Classification into potency categories is currently not a requirement in the classification of sensitizers.

RAC's response

The opinion is noted, but not supported because classification as Skin Sens. 1A cannot be excluded due to the lack of data.

Date	Country	Organisation	Type of Organisation	Comment number
13/08/2014	The Netherlands		MSCA	9

Comment received

Skin Sensitization
Current classification: Skin Sens. 1 (H317)
Proposed: Skin Sens. 1B (H317)

The Netherlands does not agree with the classification Skin Sens. 1B (H317) for Spiroxamine made by Federal Institute for Occupational Safety and Health (Germany). According to the CLP criteria: "Annex I: 3.4.2.2.1.1. Skin sensitizers shall be classified in Category 1 where data are not sufficient for sub-categorization.
Annex I: 3.4.2.2.1.2. Where data are sufficient a refined evaluation according to section 3.4.2.2.1.3 allows the allocation of skin sensitizers into sub-category 1A, strong sensitizers, or sub-category 1B for other skin sensitizers."

According to the CLP guidance this could be interpreted as: "Classification into sub-categories is only allowed if data are sufficient. Therefore care should be taken when classifying substances into category 1B when category 1A cannot be excluded. In such cases, classification into category 1 should be considered. This is particularly important if only data are available from certain tests showing a high response after exposure to a high concentration but where lower concentrations which could show the presence of such effects at lower doses are absent (in line with some test protocols where a maximized dose should be used)."

In the German proposal, an evaluation whether the available data allow exclusion of category 1A is missing and in our opinion, Category 1A cannot be excluded. This especially clear for the results of the Buehler where 58% of the animals reacted after induction with concentrations decreasing from 50% to 12%. This is close to the criteria for category 1A but dermal induction with 20% resulting in a reaction in more than 60% of the guinea pigs cannot be excluded. Similarly for the guinea pig maximization test where only a 5% induction concentration was tested and the percent responders at lower induction concentrations is not known. In this case, dermal induction with 1% resulting in a reaction with more than 60% of guinea pigs cannot be excluded. In addition, the human data do not exclude sensitization at a concentrations above 0.2% or 500 µg/m2 needed for sub-categorization.

Dossier Submitter's Response

Noted. Decision is up to ECHA/RAC

RAC's response

The opinion is noted and supported. Category 1A cannot be excluded based on available data.

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OTHER HAZARDS AND ENDPOINTS – Aquatic Environment Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22/08/2014	Belgium		MSCA	10

Comment received

Based on the reported results in the CLH dossier , the most sensitive species seems to be Skeletonema costatum with a 96hErC50 = 0.0063 mg/l and a 96hNOErC=0.00063mg/l), the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the regulation 1272/2008, as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410 . Furthermore, the substance shows very low potential to bioaccumulate.

In view of the reported results and toxicity band for acute toxicity between 0.001mg/l and 0.01mg/l, an M-factor for acute toxicity of 100 could be assigned and an M-factor for chronic toxicity of 100 (not rapidly degradable substance and toxicity band between 0.0001 mg/l and 0.001 mg/l).

However, we assume that not all available and relevant information is treated in the CLH report f.i.
- No description is given on the fate of the substance (adsorption/desorption, volatilisation)
- we presume that only the key studies for aquatic toxicity are reported in the CLH report. In order to make a correct decision on the most sensitive species and the determination of the correct M-factor , please report ALL available aquatic toxicity studies.

Was the BCF value lipid normalised? This will however not change the conclusion on bioaccumulation because the BCF is already far below 500 and based on total applied radioactivity which includes parent compound, metabolites, CO2 probably resulting in an overestimation of the BCF.

Dossier Submitter's Response

Thank you for your comments and agreement with environmental classification and labelling.

When the CLH report for Spiroxamine was initiated in 2012 it was common for all MS that only key studies had to be reported.
As far as we know the discussion process about the new format for the CLH reports, including the aspect of providing all available data for aquatic toxicity of a substance is still ongoing between ECHA and MS and not yet finalized.
Therefore we do not see the necessity to include all available data at this final stage of the CLH report/process for Spiroxamine, because provided data are most relevant and sufficient for classification and labelling.
The relevant BCF-value given in CLH report (Grau,1995) is the higher kinetic BCF value (87) based on total radioactivity and whole fish at test concentration of 20 µg/L received by BIOFAC calculation. The lower kinetic BCF value is 71 based on total radioactivity and whole fish at test concentration of 200 µg/L received by BIOFAC calculation. The steady state BCF values related to whole fish and total radioactivity are 91 and 68 for test concentration of 20 µg/L and 200 µg/L respectively. These values were unfortunately not included in CLH report of Spiroxamine.
A Normalisation to lipid content of test fishes is not possible, because there were no measurement of lipid content of the fishes in this test report. In 1995 laboratories were not obliged to do measurement of lipid content of fishes tested at BCF-studies.

RAC's response

Noted. We understand the dossier submitter's desire to minimise the amount of work necessary to justify M-factors for an existing Annex VI entry, but we agree with the comments that this additional information should normally be provided (even if only in brief summary form). The extra discussion on BCF does not affect the classification proposal.

ATTACHMENTS RECEIVED: -