Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

thiacloprid (ISO)

EC Number: N/A
CAS Number: 111988-49-9

CLH-O-0000001412-86-54/F

Adopted

12 March 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON THIACLOPRID (ISO);{(2Z)-3-[(6-CHLOROPYRIDIN-3-YL)METHYL]-1,3-THIAZOLIDIN-2-YLIDENE}CYANAMIDE

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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 some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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Substance name: thiacloprid (ISO);{(2Z)-3-[(6-chloropyridin-3-yl)methyl]-1,3-thiazolidin-2-ylidene}cyanamide
CAS number: 111988-49-9
EC number: -
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2014	Norway		MemberState	1
Comment received				
Norway would like to thank the United Kingdom for the proposal for harmonised classification and labeling of thiacloprid (ISO);{(2Z)-3-[(6-chloropyridin-3-yl)methyl]-1,3-thiazolidin-2-ylidene}cyanamide, CAS- no. 111988-49-9. We support the proposed classification for thiacloprid.				
Dossier Submitter's Response				
Thank you for the comments.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2014	Germany	Bayer CropScience	Industry or trade association	2
Comment received				
Bayer CropScience requests to review the MoA of uterine adenomacarcinoma in rat and ovarian luteoma in mouse against the offered background of scientific knowledge and thus the justification of the applied classification as Carc. Cat.3; R40 / Carc. 2; H351. **(*ECHA note: The following attachment was provided [Attachment 1]*)** Comment of Bayer CropScience Regulatory Toxicology on the proposed classification and labelling of thiacloprid as Carc. Cat.3; R40 / Carc. 2; H351				
Dossier Submitter's Response				
See response to comment 6.				
RAC's response				
RAC notes that later in the opinion development process, after the public consultation, industry communicated that they had no new data which would confirm the proposed new MoA for the uterine adenocarcinoma in rat and the ovarian luteoma in mice. Industry				

therefore concluded that the classification proposal for tumours, observed after long-term treatment with thiacloprid, should be discussed based on the original MoA as proposed by the dossier submitter (DS).

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2014	Germany		MemberState	3
Comment received				
The DE CA supports the proposal of the UK CA for harmonized classification and labeling of Thiacloprid, with the exception of classification as Repr. 2; H361f. Furthermore, we recommend changing the IUPAC name in chapter 1.1 to (Z)-N-{3-[(6-Chloro-3-pyridinyl)methyl]-1,3-thiazolidin-2-ylidene}cyanamide.				
Dossier Submitter's Response				
Thank you for the comments, these are noted. We can agree to the suggested IUPAC name.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2014	Sweden		MemberState	4
Comment received				
The information in the human health section is not detailed enough to assess the general systemic toxicity that is claimed to explain other effects observed.				
Dossier Submitter's Response				
Noted. However, we consider that the report does contain enough information to enable an assessment of general systemic toxicity to be made. Further information is provided in light of the specific comments below.				
RAC's response				
Noted. However, RAC considers that the CLH report contains sufficient information to enable an assessment of general systemic toxicity.				

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2014	Spain		MemberState	5
Comment received				
The Spanish CA agrees with the United Kingdom´s proposal for harmonised classification and labelling. In addition to the proposed classification, the potential as an endocrine disruptive should be highlighted. Thiacloprid interferes with sex hormone biosynthesis producing prolonged perturbation of sex hormones in the long term toxicity, carcinogenicity and reproductive toxicity studies.				
Dossier Submitter's Response				
Thank you for the comments. It is correct that thiacloprid interferes with sex hormone biosynthesis. The classifications proposed for carcinogenicity and reproductive toxicity have been based on the reported increased incidence of tumours and functional effect on reproductive performance, as classification for human health is not based merely on the fact				

of a substance being an endocrine disruptor. As such, it was decided it was not necessary to highlight the endocrine disruption potential of thiacloprid in the CLH report.
RAC's response
The potential of thiacloprid to cause hormonal imbalance is well taken into account by the DS in the assessment of the effects of thiacloprid. It is also highlighted in the RAC opinion.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2014	United Kingdom	Bayer CropScience	Industry or trade association	6
Comment received				
The carcinogenicity classification and labelling needs to be reconsidered in my opinion (see attached document)as the mechanism of action for the uterine tumours is not relevant for man.pp41,47, 52 **(*ECHA note: The following attachment was provided [Attachment 2]*)** Review of the Thiacloprid rodent carcinogenicity studies regarding increased incidences of tumours in the female genital tract, Prof.Dr. J.H.Harleman DVM, PhD, ERT, FIATP				
Dossier Submitter's Response				
Thank you for this additional information, which was not available to the dossier submitter during the preparation of the CLH proposal. As such, we have not considered the relevance of this proposed mode of action to thiacloprid in depth, but have the following brief comments. Uterine tumours in rats. Some features of the findings with thiacloprid showed a pattern that was compatible with the proposed reduction in prolactin. Whilst the incidences of uterine tumours were increased, those of mammary gland and pituitary gland tumours were reduced or similar to controls. The thiacloprid carcinogenicity study in rats was conducted in the Wistar strain, which has been reported to show an inverse relationship between mammary and uterine tumours (Harlemann *et al*., *Toxicol. Pathol*. 2012, **40**, 926-930). Harlemann *et al*. (2012) reported that prolonged inhibition of prolactin results in an increased oestradiol:progesterone ratio, a feature that was observed upon thiacloprid administration. When thiacloprid was administered to aged female rats (2009e), the incidence of repetitive pseudopregnancy was reduced, which also appears to be consistent with a reduction in pituitary prolactin release (Harlemann *et al*., 2012). However, there are also some inconsistent findings. Hargreaves and Harlemann (*J. Appl. Toxicol.* 2011, **31**, 599-607) state that prolonged bromocriptine administration results in a treatment-related decrease in food intake/body weight gain in both sexes, whereas with thiacloprid, body weight was reduced only in the females in the rat carcinogenicity study. Although increased incidences of uterine tumours occurred together with a maximum reduced body weight of 21% in females in the high-dose group, increased incidences of uterine tumours were also reported in the mid-dose group, when the maximum decrease in body weight was 15%; it is not clear if a decreased body weight of up to 15% would be sufficient to invoke the sustained lower levels of prolactin postulated in attachment 2 to be responsible for the uterine tumours. Hargreaves and Harlemann (2011) describe other possible characteristics of decreased prolactin levels that were not observed with thiacloprid: reduced chronic progressive nephropathy in males; increased Leydig cell hyperplasia / neoplasia; implantation failure and reduced fertility in females.				

There was no direct evidence that thiacloprid induced uterine tumours through this mode of action. Although prolactin levels were reported in one study (CAR 6.10 (1998; and 1998b)), there was much intra-group variability, with overlapping confidence intervals between control/treated comparison groups and only a small number of samples in some groups. As acknowledged in attachment 2, the study was not well designed for the measurement of prolactin levels, and overall one should be careful about drawing conclusions from these results.

Luteomas in mice. An involvement of prolactin in the induction of luteomas in mice is speculative, and it is acknowledged in attachment 2 that the relevance of these tumours to humans is unclear (and therefore should not be dismissed).

RAC's response

See reply to comment 2.

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2014	Germany	Bayer CropScience	Industry or trade association	7

Comment received

Bayer CropScience requests to review the MoA of uterine adenomacarcinoma in rat and ovarian luteoma in mouse against the offered background of scientific knowledge and thus the justification of the applied classification as Carc. Cat.3; R40 / Carc. 2; H351.

(*ECHA note: The following attachment was provided [Attachment 1]*)

Comment of Bayer CropScience Regulatory Toxicology on the proposed classification and labelling of thiacloprid as Carc. Cat.3; R40 / Carc. 2; H351

Dossier Submitter's Response

See response to comment 6.

RAC's response

See reply to comment 2.

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2014	Sweden		MemberState	8

Comment received

Page 51: Development of different types of tumors was observed in two species; ovarian tumors in mice and uterine and thyroid tumors in rat. These apparently developed as a consequence of an altered hormonal secretion pattern (according to the mechanistic studies included). In rats, the tumors occurred at doses where systemic toxicity was observed but this was not the case in mice.
The UK CA propose classification in category 2 rather than 1B since the malignant uterine tumors were only observed at doses with severe systemic toxicity (reduced bodyweight 15-20% and histopathological degenerative changes), the tumors were mainly benign and not statistically significant and the mechanism seemed to be due to hormonal disturbance and not to a genotoxic action.
In our view, the systemic toxicity observed does not explain the tumors which apparently

developed due to a fairly specific mechanism (i.e. a hormonal disturbance leading, according to the applicant, to an exacerbation of the ageing process). If this would be a secondary effect due to poor condition of the animals, these tumor types (among which ovarian luteomas is stated to rarely occur in mice) would commonly be observed in carcinogenicity studies when animals are tested at the MTD. In our experience, this is not the case.
According to the CLH report, the frequencies of uterine adenocarcinomas were well above the historical control value and outside of the range in the laboratory. Even though statistical significance was not achieved in pair-wise comparisons, the uterine adenocarcinomas induced a highly significant trend (p=0.0005) which is a stronger indication of the relevance of an effect. The increased frequency of thyroid follicular cell adenoma in male rats were statistically significant at the highest two doses and the frequency of benign ovarian luteomas in mice was above historical control data at the two highest doses.
Since both benign and malign uterine tumors (rat) and ovarian tumors (mice) were observed, it is reasonable to assume that benign tumors may progress to malignancy. The frequency of malignant adenocarcinomas (6, 3, 3, 14,18/50 at 0, 1.6, 3.3, 33.5, 69.1 mg/kg bw/d was higher than the frequency of benign adenoma (0, 0, 1, 1, 2/50). The frequency of malignant adenosquamous carcinoma was 0, 0, 0, 1, 2/50 at 0, 1.6, 3.3, 33.5, 69.1 mg/kg bw/d.
Finally, even if one of the three tumor types observed would be of less relevance for humans (e.g. the thyroid follicular cell adenoma), the substance yet seems to have an intrinsic potential to alter the hormonal secretion pattern in at least two species and it can thus not be excluded that a tumorigenic response could occur also in humans, although the affected tissue may be different.
For these reasons, the Swedish CA proposes that classification in category 1B should be considered.

Dossier Submitter's Response

Thank you for your careful consideration of the data.

Increased incidences of malignant uterine tumours in rats were only observed alongside toxicity that indicated that the maximum tolerated dose had been achieved or exceeded. In these animals, body weights were reduced by 15 – 20 % and histopathological changes were noted which included degenerative myelopathy in the nervous system characterised by radiculoneuropathy, sciatic nerve degeneration and subsequent skeletal muscle atrophy. In the eyes, retinal atrophy and lens degeneration were noted. Likewise, the ovarian tumours in mice occurred at doses that were associated with histopathological changes in the liver, including necrosis. It is generally accepted that tumours that occur only at excessive doses, associated with severe toxicity, have a more doubtful potential for carcinogenicity in humans. If such a confounding effect of excessive toxicity is suspected, a classification in Category 2 rather than 1B is supported.

Another consideration is the tumour type and background incidence. Apart from a single malignant ovarian tumour, the luteomas observed in female mice were benign and the increased incidence was not statistically significant, although it was slightly above the historical control range from the same laboratory. Additional historical control data suggests that incidences of this tumour type are often clustered within studies. In terms of the rat uterine tumours observed, historical control data from Wistar rats indicates that uterine tumours tend to be malignant rather than benign; therefore, although the CLP guidance suggests that malignant tumours usually constitute sufficient evidence for Category 1B, we do not consider that this applies in the case of the uterine tumours. In terms of the statistical analysis of the uterine adenocarcinomas, we acknowledge in the CLH report that

the trend test was highly significant (P = 0.0005), whereas a pair-wise comparison of control and high-dose group resulted in a P value of 0.054. We also note that, although the study authors reported these findings as not being of statistical significance, it should be borne in mind that the incidence in the control group was relatively high (12%, being double that of the two lowest dose groups), which would have affected this P value. The absence of evidence for a genotoxic mechanism of action lessens the level of concern for humans. The most likely mechanism of action, at least for the uterine tumours, was a secondary one through the prolonged perturbation of sex hormones; this mechanism is associated with a threshold effect, which is further evidence that the lower classification is the most appropriate, in accordance with the CLP guidance (section 3.6.2.3.2). Taking into account the overall tumour profile in rats and mice, classification as a Category 2 carcinogen according to the CLP criteria is judged to be most appropriate.
RAC's response
The overall assessment of the available data leads to a conclusion for Category 2 as proposed by the DS. The rationale is presented in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2014	Belgium		MemberState	9
Comment received				
We agree with the carcinogenic classification proposal in category 2. ☐ In CAR A6.5/6.7 (1998), in rats, the results reveal an increased incidence of uterine adenocarcinoma at 500 and 1000 ppm (corresponding to 25.2 and 51.7 mg/kg in males and 33.5 and 69.1 mg/kg in females, respectively). Malignant uterine adenocarcinoma was reported in 6 female controls, in 3 treated at 25 ppm, in 3 at 50 ppm, in 14 at 500 ppm and in 18 at 1000 ppm. These results are not statistically significant however the incidence was above the mean historical control value. In both sexes, an increase in the incidence of thyroid follicular cell adenoma was also showed. At these dose levels, severe toxic effects were presented (decrease body weight 15-20%, histopathological changes in liver and thyroid, increase prevalence of skeletal atrophy and sciatic nerve degeneration…) ☐ In CAR A6.7 (1998), the treated female mouse showed an increase in benign ovarian luteomas. There was no evidence of thyroid or uterine tumours. The target organ were different in the 2 studies conducted in 2 different species. None of the findings was statistically significant and in the same time above the historical control data.				
Dossier Submitter's Response				
Thank you for the comments, these are noted.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2014	Belgium		MemberState	10
Comment received				
We agree to classify in category 2 for the reproductive toxicity. Thiacloprid induces dystocia in CAR A6.8.2 (1995). This finding was associated with a decrease in bodyweight, an increase in liver weight and hepatocyte hypertrophy, … These effects were not pronounced				

and then they don't modify the classification (In the Guidance on the application of the CLP criteria : "There is no established relationship between fertility effects and less marked systemic toxicity. Therefore, it should be assumed that effects on fertility seen at dose levels causing less marked systemic toxicity are not secondary consequence of this toxicity").
Dossier Submitter's Response
Thank you for the comments, these are noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2014	Germany		MemberState	11
Comment received				
These concerns regarding Repr. 2 were stated in the first commenting period in 2010. The DE CA does not support to classify Thiacloprid for fertility effects (H361f) according to CLP regulation criteria due to the following reasons: Dystocia was observed in rats in several studies, but only when the substance was incorporated in the feed and not when high toxic doses where given by gavage near parturition. In addition, the finding was restricted to a few dams in each study and there was inconsistency between the F0 and the F1 generation in the two-generation study for this effect. Dams that exhibited dystocia also showed minimal to moderate liver necrosis, a finding that was lacking in the dams that delivered successfully. The combination of these findings would indicate that there is no direct effect on the birth process and some other toxicity or condition that requires prolonged exposure at high doses needs to be present before dystocia occurs. The increases in progesterone and corticosterone measured in rats as well as the histopathological findings in adrenals and ovaries of mice point to an inhibition of 20α-hydroxysteroid dehydrogenase, an enzyme involved in the catabolism of progesterone and 11-deoxycorticosterone and in the control of progesterone homeostasis during pregnancy and before parturition in rodents. We suggest that the finding of dystocia was not relevant for humans because parturition is induced differently in rats and humans (c.f. change in progesterone levels).				
Dossier Submitter's Response				
Thiacloprid administration to Sprague-Dawley (Sasco) rats resulted in problems with parturition that had serious toxicological consequences. The historical data on Wistar and Sprague-Dawley (Sasco) rats (Table 22) show that the incidence of dystocia was largely unaffected by administration of the test substances, even when the animals received doses that resulted in toxicity. This was in striking contrast to the situation with thiacloprid, in which dystocia only occurred in animals that received doses that resulted in toxicity. When the high-dose groups were compared, the incidence of dystocia per animal, per generation and per study was markedly higher in the thiacloprid studies than in the studies on other substances (6.7 % of animals in the studies conducted at Stilwell, compared with 0.94 % of Sprague-Dawley (Sasco) rats in the non-thiacloprid studies). There is no reason to suppose that the animals in the thiacloprid studies suffered more non-specific stress than those in the other studies. The data suggests that something specific to thiacloprid administration was involved in the induction of dystocia.				

In the study CAR A6.8.2 (1997), dystocia occurred in conjunction with liver necrosis, since all dams with dystocia also showed a degree of hepatocellular necrosis; in contrast, no liver necrosis occurred in P dams that delivered normally. The repeated dose studies demonstrated that the liver is a target organ of thiacloprid. Liver hypertrophy (slight to moderate) was reported in those animals in the study (2011c) in which dystocia occurred, but it also occurred (graded minimal to moderate) in the majority of dosed animals that did not have dystocia (reported in 25/26 treated animals). Hepatocellular necrosis was not reported in this or any of the other reproductive studies, although histopathology of the liver was not always included in the investigations. An association between increased incidence and/or severity of liver toxicity and dystocia has therefore not been demonstrated.

In only one study report was dystocia presumed to be a non-specific consequence of maternal toxicity (CAR A6.10 (1998d)). In this study, thiacloprid was administered at a dose of 100 mg/kg/d on GD 18 and 19, then because of excessive toxicity the dose was reduced to 50 mg/kg/d on GD 20; the one case of dystocia recorded was considered by the authors to be associated with necrosis of a uterine horn and general maternal toxicity rather than a direct effect on the birth process. In all the other studies, lower doses were administered. Overall, the conclusion is that general maternal toxicity by itself does not lead to dystocia in the Sprague-Dawley (Sasco) rat.

We conclude that the consistent finding of dystocia, without unequivocal information on a mode of action to indicate that it is not relevant to humans, is of sufficient concern to merit classification in Category 2 (H361f).

RAC's response

RAC takes note of this opinion, but the rationale for classification in Category 1B is presented in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2014	Sweden		MemberState	12

Comment received

Page 71: We appreciate the systematic and comprehensive discussion of the data for the endpoint toxicity to reproduction.
We agree that a disturbance of the estradiol/progesterone ratio seems to be a possible mechanism behind the dystocia observed in several rat studies. However, the mechanistic studies are difficult to interpret since in some cases the doses are reported as a concentration (in molar) which is difficult to compare with doses in standard studies (reported in mg/kg bw/d) and in other cases the lowest dose tested in the mechanistic studies is yet higher than the lowest dose where dystocia was observed (i.e. 3.7 mg/kg bw).
The UK CA propose classification in category 2 rather than 1B since dystocia was observed at maternally toxic doses (liver toxicity, reduced body weights, pallor, hypoactivity), the mechanistic studies did not clearly indicate relevance of the proposed mode of action for humans and the incidence of dystocia was rather low.
In our view, the data does not convincingly show that the effects observed are secondary consequences of maternal toxicity. In the two-generation study (CAR A6.8.2 (1997)), the gestational body weight gain (day 0-20) was only reduced by 6% (n.s.s) in high dose F0 dams and the body weight gain in the other treated groups was in fact higher than in controls. The body weight was reduced by 6 and 5% at days 20 and 0 in high dose groups otherwise no statistically significant difference was observed except the body weight in mid dose animals at day 0 (5% reduction). The body weight gain in F1 dams was not

statistically significantly different from controls and only in the high dose F1 animals, a statistically significant reduced body weight was observed at day 0 and 20 (9 and 7% respectively). In our view this is no evidence of maternal toxicity end even if this had been the case, the effect observed would be a specific rather than a non-specific effect We do not agree that the proposed mode of action probably lessens the concern for humans. Even if the mechanism indeed is a disturbance of the E/P balance, in rats expressed as the specific effect dystocia, we do not know what the biological consequence of this disturbance would be for humans. This need to be further discussed. Moreover, an increase of the number of stillbirths in F1 and F2 were observed. This does not seem to be a consequence of dystocia since this was not observed in F2 females and an increased number of stillbirths were also observed in the one-generation (range-finding) study in which no dystocia was observed. For these reasons, the Swedish CA proposes that classification in category 1B should be considered.
Dossier Submitter's Response
As we note in the CLH report, adverse effects on parturition were only recorded at doses of thiacloprid that were maternally toxic in other ways that were unrelated to the proposed mode of action (liver toxicity, reduced body weights compared with controls, pallor, hypoactivity). The parturition problems did not occur at non-maternally toxic doses. Another consideration is that the mechanistic information did not clearly demonstrate relevance of the proposed mode of action to humans. Rather, it is more likely to lessen the level of concern for humans: parturition in humans does not seem to be as tightly regulated as it is in rodents and it has been proposed that there is redundancy in the control of human parturition, such that if one pathway is disrupted, others can compensate. In further support of the lower classification, the incidence of adverse effects on parturition was rather low: of the studies conducted at Stilwell, the overall mean animal incidence of dystocia in high-dose groups with toxicity was 6.7 %. Overall, we consider that Category 2 (H361f) is the most appropriate classification.
RAC's response
RAC takes note of this opinion and support the Swedish CA conclusion for Category 1B. The rationale is presented in the opinion.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2014	Belgium		MemberState	13
Comment received				
We support the classification Acute Toxicity category 3 via oral and category 4 inhalation routes based on the following results : ☐ Via oral route : One study (CAR A6.1.1 (1996a)), in compliance with OECD 401 guideline, indicated a LD50 of 444 mg/kg in females and another study, CAR A6. 9 (1997), in compliance with US-EPA guideline, showed a calculated LD50 of 177mg/kg in females. The lowest value fulfills the criteria for category 3 (50-300 mg/kg).and then we support the DS classification proposal. ☐ Via inhalation route : LC50 of 1.2 mg/l in females (CAR A6.1.3 (1996)) fulfills the criteria for category 4 (1-5 mg/l) then we support the DS classification proposal.				
Dossier Submitter's Response				
Thank you for the comments, these are noted.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2014	Spain		MemberState	14
Comment received				
The Spanish CA supports the proposed classification of thiacloprid as T; R25 under Directive 67/548/EEC and as Acute Tox. 3 (H301: toxic is swallowed) under Regulation (EC) 1272/2008. The results of the range finding acute neurotoxicity study (LD50 calculated: 177 mg/kg p.c.) support this classification. The Spanish CA supports the proposed classification of thiacloprid as Xn; R20 under Directive 67/548/EEC and as Acute Tox. 4 (H332: harmful if inhaled) under Regulation (EC) 1272/2008; based on the calculated CL50 = 1.2 mg/l in females. For clarity, Spanish CA considers that the percentage of mortality in females should be included on table 11.				
Dossier Submitter's Response				
Thank you for the comments, these are noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2014	Sweden		MemberState	15
Comment received				
Page 37: Clinical signs of neurotoxicity were observed at all dose levels in all oral acute toxicity studies in rats tested at doses above 11 mg/kg bw. The effects occurred also at dose levels where no mortality or other signs of general toxicity were observed. A specific effect on the nervous system is consistent with the mode of action of the substance. According to the study summaries (CAR) neurotoxic effects such as poor reflexes, impaired motor and locomotor activity, decreased, spastic gait, tremor, convulsions etc. were observed up to 6 days post treatment. Surprisingly no neurotoxic effects seemed to occur in repeated dose studies, possibly due to a difference in administration route (gavage/inhalation versus diet). We consider the observed effects severe, i.e. significant functional changes, and the effects more than transient in nature since they occur up to six days after treatment. The CLP states that significant functional changes, more than transient in nature, should be taken into consideration for a decision on classification STOT-SE (3.8.2.1.7.3 (b)). Therefore, we welcome a discussion at RAC to consider classification in STOT-SE.				
Dossier Submitter's Response				
Thiacloprid acts as a selective nicotinic acetylcholine receptor agonist. The potential neurotoxicity of the substance has been investigated in rats after both oral gavage and dietary administration. In the CAR, it was concluded that substance-related effects in the study (CAR A6. 9 (1997)) were non-specific acute clinical signs that had resolved by the next observation period (7 days); as there was no earlier observation period, it is not known if the effects had resolved much earlier than this, and so it is not possible to state that they were not transient. It is not clear why decreased motor and locomotor activity were observed after a single dose but there were no signs of neurotoxicity after repeated				

exposure of the same doses. Moreover, the effects observed were likely related to the toxicity that resulted in death of the animals at higher doses, for which a classification for acute oral toxicity has been proposed. Therefore, we consider that a classification for STOT-SE is not required.
RAC's response
In acute neurotoxicity tests, some effects such as decreased motor activity and locomotor activity occurred at doses 10-fold below the dose causing lethality and in the absence of other signs of toxicity. However, they are considered as transient since they were reversible and not observed in longer term studies. These kind of effects support STOT SE Category 3 and RAC hence proposes to classify thiacloprid as STOT SE 3.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2014	Sweden		MemberState	16
Comment received				
Page 39: Retinal atrophy was observed in treated rats in the carcinogenicity study. The frequency was statistically significantly higher in treated animals (24/50*, 25/50* and 32/50** at 3.3, 33.5 and at 69.1 mg/kg bw/d respectively) compared to controls (15/50). An increased frequency of lens degeneration was observed at the two highest dose levels in the same study (20/50** at 33.5 and 30/50** at 69.1 mg/kg bw/d) and these increases were statistically significantly higher than controls (9/50). In our view, the retinal atrophy which occurred at a dose below the (adjusted) guidance value and is an effect that may cause blindness seems to fulfill the description in point g) "Evidence of appreciable cell death (including cell degeneration and reduced cell numbers) in vital organs incapable of regeneration". Therefore, we propose that classification STOT-RE should be taken into consideration.				
Dossier Submitter's Response				
In the two-year carcinogenicity study, degenerative myelopathy and degeneration of the lens occurred from 33.5 mg/kg/d in females. When the oral guidance value is adjusted from a 90-day study to one of 24-months' duration, a value of 12.5 mg/kg/d is obtained, which is clearly below the dose at which degenerative myelopathy and degeneration of the lens were reported. Additional considerations are that these effects only occurred after chronic exposure; some of the findings associated with the degenerative myelopathy are known to occur in aged rats and can be exacerbated by xenobiotics; and the degeneration of the lens was present in many control animals. Therefore, these two effects were not considered further in deciding upon a classification for repeated-dose toxicity. A statistically significantly increased incidence of retinal atrophy was reported in a two year study in rats from 3.3 mg/kg/d; however, there was also a high incidence in the control animals (15/50). A chronic exposure seemed to be necessary to induce this effect, since it was not seen after 90 days or one year of administration. No neurological effects occurred in a two-year mouse study in which thiacloprid was administered at doses up to 873 mg/kg/d. On balance, we decided that this finding did not provide a sufficient basis to justify the classification of thiacloprid for repeated dose toxicity.				
RAC's response				
RAC support the justification for no classification by the DS for this effect.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment

				number
20.03.2014	Belgium		MemberState	17
Comment received				
Based on the results of the aquatic toxicity test on the most sensitive species, which spend most of their sensitive life stage in the water phase, (Ecydonurus sp with 48hEC50 = 0.0077 mg/l, Chironomus riparius with 28dNOEC=0.0005mg/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 low potential to bioaccumulate. In view of the proposed classification 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 0.0001mg/l and 0.001 mg/l). In conclusion : we agree with the proposed environmental classification by the UK. Some editorial or/and minor comments : Acute tox : Ecydonurus sp.,(OECD202), Manson2002d The acute toxic effects on the mayfly Ecydonurus sp. were tested following OECD guideline 202. This guideline recommends the use of at least 20 animals, preferably divided into four groups of five animals each, at each test concentration and for the controls. In this test only 10 animals were used, 10 groups of 1 animal, weakening the statistical power as this is sample size dependant. The EC50 will tend to be higher in studies with smaller numbers of animals per dose group. However Ecydonurus is found to be the most sensitive species for acute aquatic toxicity. Furthermore the measured concentration for the lowest dose tested (0.004mg/l) was <80% of the nominal. Notwithstanding the fact that it will not affect the order of magnitude of the EC50 it would have been better to use the measured concentration to determine the EC50.				
Dossier Submitter's Response				
Thank you for the comments, these are noted and acknowledged. However, they do not affect the proposed classification or M-factors - see also measured 48h EC50 for *Ecydonurus* of 0.006 mg/L identified by DE in subsequent comment (18).				
RAC's response				
Noted and acknowledged.				

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2014	Germany		MemberState	18
Comment received				
Page 80 Table 36: summary of relevant aquatic toxicity information on technical Thiacloprid There is a minor mistake in the results of toxicity to Hyalella azteca (Bowers, 1996) EC50 (96h) = 0.0245 mg/L measured instead of 0.0407 mg/L measured. There is a minor addition in the results of toxicity to Ecydonurus sp. (Manson, 2002d) EC50 (48h) = 0.006 mg/L measured. There are additional relevant acute and chronic data for the saltwater mysid Mysidopsis bahia (Drottar and Swigert, 1996) available: LC50 (96h) = 0.031 mg/L nominal (flow-through system) NOEC (32 d) = 0.001 mg/L nominal (flow-through system) Page 87 comparison with criteria for environmental hazards:				

Instead of application of the surrogate approach using acute data for Ecydonurus sp. for chronic classification of Thiacloprid we would prefer to use results of the valid chronic chironomid study (NOEC = 0.0005 mg/L).
Dossier Submitter's Response
The data indicate that the EC50 of 0.0407 mg/L for technical thiacloprid quoted in the CLH report and DAR was based on immobility of *Hyalella*, a standard measure of acute toxicity for aquatic invertebrates. The EC50 of 0.0245 mg a.s./L was based on the number of 'floaters' at the surface in test vessels (a sublethal parameter). As it is not clear how to interpret this mechanism in relation to classification, it is proposed to rely on the existing immobility endpoint. We acknowledge presentation of the 48h EC50 for *Ecydonurus* as the slightly lower 0.006 mg/L measured endpoint (see also BE comment on this). Neither this nor the alternative *Hyalella* endpoint affect the aquatic classification proposals. The additional mysid data were not included in the DAR or subsequently made available to the UK CA at the time the Report was written. Their reliability in this respect has not therefore been ascertained; however, assuming they are valid would not affect the overall aquatic classification proposals. The UK presented both the surrogate approach using the acute *Ecydonurus* endpoint and use of the chironomid endpoint as supporting the same overall Chronic 1 classification and M-factor. Whilst the *Ecydonurus* study might not be ideal (see BE comment) it was considered reliable and relevant for classification. This most acutely sensitive species was also not used in chronic tests, so the surrogate approach should be considered. There were also uncertainties interpreting the chironomid endpoint for classification, nevertheless it was considered reliable too. We prefer to take account of both approaches, however acknowledge that RAC may wish to define a single endpoint for chronic classification.
RAC's response
RAC agrees with the DS's explanation regarding the result in the Hyalella test. RAC agrees that in the Ecydonorus test the result should be expressed as measured concentration. RAC agrees with the DS comment on the new data. RAC is of the opinion that the basis for chronic classification should be the acute Ecydonorus test result and that the Chironomus test result should only be used as supportive evidence because in the OECD 219 test the organisms might also be exposed via sediment.

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2014	Sweden		MemberState	19
Comment received				
The Swedish CA supports the UK CA environmental classification proposal (Aquatic Acute 1, Aquatic Chronic 1 with an Acute and Chronic M factors of 100) of thiacloprid (CAS nr 111988-49-9) based on Regulation (EC) 1272/2008. Degradation Thiacloprid is not readily biodegradable as 0% biodegradation was observed after 28 days according to OECD guideline 301 F. Based on the water solubility and aquatic micro-organism tests, biodegradation was not limited by solubility or micro-organism toxicity. Thiacloprid exhibits primary aerobic degradation in the aquatic environment with a DT50 that varies between two water-sediment test systems with 20.3-27.9 days and 10.7-12.1 days, depending on sediment type. Since only one of these is below the 16 days, these data are not sufficient for thiacloprid to be considered as rapidly degradable. On this basis, thiacloprid is not considered to undergo rapid and ultimate degradation, and				

not considered to be rapidly degradable for the purposes of classification.

Bioaccumulation
Based on the low measured log Kow values (0.73 and 1.26) thiacloprid is considered to have a low bioaccumulation potential in aquatic organisms.

Aquatic toxicity - Acute toxicity
Thiacloprid is acutely toxic to fish (Oncorhynchus mykiss and Lepomis Macrochirus), with a lowest 96 h LC50 of 25.2 mg/l.

For the water flea Daphnia magna no acute toxicity was observed (48-h EC50 > 85.1 mg/l). However, a significant acute toxicity was seen for other invertebrates: acute EC50 values below 1 mg/l were observed for Asellus aquaticus (freshwater hog louse), Gammarus pulex (freshwater shrimp), Ecydonurus sp. (mayfly larvae) and Hyalella azteca (freshwater amphipod).
The lowest observed acute result is a 48 h EC50 of 0.0077 mg/l for Ecydonurus sp. Larvae based on mortality and immobilisation. This value indicates significantly higher sensitivity than for Daphnia magna, and around an order of magnitude greater sensitivity than the other invertebrates.

Thiacloprid is an insecticide and it would be expected that thiacloprid has a toxic effect on a wide range of insects. It is therefore appropriate to use the results for the most sensitive aquatic insects even though they might not be a 'standard' test organism. This result is considered acceptable for classification purposes and also in according to the ECHAs Guidance on the application of CLP criteria, Nov. 2012.

Thiacloprid is less acutely toxic to plants than fish and invertebrates, the lowest 72 h ErC50 for algae being 96.7 mg/l and a 15 d EC50 of >95.4 mg/l for aquatic macrophytes

Aquatic toxicity - Chronic toxicity:
Chronic aquatic toxicity data for fish and Daphnia are of a similar order of magnitude, the most sensitive result being a 97-d NOEC of 0.244 mg/l for fish; algal and aquatic macrophyte NOECs are above 1 mg/l. No chronic data are available for the most acutely sensitive species Ecydonurus sp. A 28 d study using another insect species, Chironomus riparius, is available, with a NOEC of 0.0005 mg/l. There is some uncertainty whether the organisms were exposed mainly via sediment rather than water, so whilst the result has been used for risk assessment purposes in the CAR, it is considered as supporting information for classification purposes(in according to the ECHAs Guidance on the application of CLP criteria , Nov. 2012)

Aquatic toxicity - M-factor:
The acute aquatic toxicity data showed a L(E)C50 value below 1 mg/l and therefore a classification in Aquatic Acute 1 is applicable. With a EC50 for Ecydonurus sp. of 0.0077 mg/l an acute M-factor of 100 is appropriate (since 0.001 < L(E)C50 <= 0.01 mg/l). A full set of chronic data for the three trophic levels is available, although the most acutely sensitive species is not represented. Based on the most sensitive standard test organism data (97 d NOEC of 0.244 mg/l for fish), and lack of rapid degradability, the substance would be classified as Aquatic Chronic 2. However, based on the surrogate approach (according to the ECHAs Guidance on the application of CLP criteria , Nov, 2012) using the Ecydonurus sp. 48 h EC50 result and lack of rapid degradation, classification in Aquatic Chronic 1 is appropriate with an M-factor of 100 (since 0.001 < L(E)C50 <0.01 mg/l). The same classification and M-factor are also suggested by the toxicity study with Chironomus riparius, (0.0001 <NOEC <= 0.001 mg/l), although as there is some uncertainty about

exposure routes in the test, it is not the key data for chronic classification. The same classification is also indicated by the acute toxicity data for other aquatic invertebrates.
Dossier Submitter's Response
Thank you for the comments, these are noted. The assessment concurs with that of the UK CA and supports the environmental classification proposal.
RAC's response
Thank you for the summary. RAC agrees with the conclusions.

ATTACHMENTS RECEIVED

1. Comment of Bayer CropScience Regulatory Toxicology on the proposed classification and labelling of thiacloprid as Carc. Cat.3; R40 / Carc. 2; H351, Submitted by Bayer CropScience on 21.03.2014 [Filename: Comment of Bayer CropScience Regulatory Toxicology_21314] [*Please refer to comment 2 and 7*]

2. Review of the Thiacloprid rodent carcinogenicity studies regarding increased incidences of tumours in the female genital tract, Prof.Dr. J.H.Harleman DVM, PhD, ERT, FIATP, Submitted by Bayer CropScience on 21.03.2014 [Filename: ReviewThiaclopridHarlemanv2 final] [*Please refer to comment 6*]