Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

thiamethoxam (ISO); 3-(2-chloro-thiazol-5-ylmethyl)-5-methyl[1,3,5]oxadiazinan-4-ylidene-N-nitroamine

EC Number: 428-650-4
CAS Number: 153719-23-4

CLH-O-0000006724-70-01/F

Adopted

5 December 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON THIAMETHOXAM (ISO); 3-(2-CHLORO-THIAZOL-5- YLMETHYL)-5- METHYL[1,3,5]OXADIAZI NAN-4-YLIDENE-N- NITROAMINE

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 comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. 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. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: thiamethoxam (ISO); 3-(2-chloro-thiazol-5- ylmethyl)-5-methyl[1,3,5]oxadiazi nan-4-ylidene-N- nitroamine
EC number: 428-650-4
CAS number: 153719-23-4
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Spain		MemberState	1
Comment received				
2.6.5.3 Conclusión on classification and labelling for carcinogenicity In mice, neoplastic alterations were observed in the liver at 500 ppm (63.8-87.6 mg/kg bw/day males and females, respectively). The available data provide evidence to support the postulated MoA (liver tumours in mice induced through sustained cytotoxicity and subsequent regenerative hyperplasia induced by a hepatocyte cytotoxicant metabolite). The metabolic activation of thiamethoxam in rats appears to be quantitatively lower than in mice and no tumours are produced in rats treated with thiamethoxam at dose levels up to 1500ppm during 24 months. Likewise, in human cells the metabolic activation of thiamethoxam appears to be quantitatively far much lower than in mouse cells. Therefore, the progression of key events cannot occur in rats and humans because of insufficient metabolic rate to generate enough amount of hepatocyte cytotoxicant. On overall, human relevance of the mode of action can reasonably be excluded on the basis of marked quantitative differences in metabolism between mice and humans. Therefore, the Spanish CA agrees with the dossier submitter that thiamethoxam is not expected to cause hepatic tumours in humans.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Carcinogenicity was not open for public consultation and has not been assessed by RAC.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON THIAMETHOXAM (ISO); 3-(2-CHLORO-THIAZOL-5- YLMETHYL)-5- METHYL[1,3,5]OXADIAZI NAN-4-YLIDENE-N- NITROAMINE

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Belgium		MemberState	2
Comment received				
BE CA would thank the FR CA for this CLH dossier proposal and agree not to classify thiamethoxam for acute toxicity via dermal route and via inhalation route. However, BE CA regrets that the carcinogenicity endpoint is not open to comment.				
Dossier Submitter's Response				
FR, as RMS of the renewal of the approval of thiamethoxam under PPP regulation, has prepared a combined CLH/RAR report in which all the end points have been discussed against CLP criteria. Syngenta has decided to withdraw thiamethoxam from the active substance renewal process before the commenting period had been launched. Therefore, other member states could not have the opportunity to comment the RMS position within the peer-review process under Regulation (EU) No 1107/2009. As regard, the harmonised classification process, ECHA has decided that based on the information provided in the CLH report and the type of proposal and substance the following hazard classes will be opened for comments during public consultation (PC) and evaluated by RAC: • Flammable solids • Reproductive Toxicity • Hazards to the Aquatic Environment				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.03.2019	Denmark		MemberState	3
Comment received				
-				
Dossier Submitter's Response				
-				
RAC's response				
-				

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	Germany		MemberState	4
Comment received				
Considering adenoma and adenocarcinoma in mice, the mode of action analysis provided should be considered by RAC.				
Dossier Submitter's Response				
FR, as RMS of the renewal of the approval of thiamethoxam under PPP regulation, has prepared a combined CLH/DRAR report in which all the end points have been discussed against CLP criteria. Syngenta has decided to withdraw thiamethoxam from the active substance renewal process before the commenting period had been launched. Therefore, other member states could not have the opportunity to comment the RMS position within the peer-review process under Regulation (EU) No 1107/2009. As regard, the harmonised classification process, ECHA has decided that based on the information provided in the CLH report and the type of proposal and substance,				

Reproductive Toxicity will be the only hazard class regarding human health to be opened for comments during public consultation (PC) and evaluated by RAC.
RAC's response
RAC has not evaluated carcinogenicity for reasons explained by the DS.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
11.03.2019	Denmark		MemberState	5
Comment received				
DK suggests that the proposed classification should be at least: Repr.2 H361.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you, noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Austria		MemberState	6
Comment received				
AT CA (Biocides): Comment on Thiamethoxam (ISO); 3-(2-chloro-thiazol-5- ylmethyl)-5-methyl[1,3,5]oxadiazi nan-4-ylidene-N-nitroamine concerning the proposed classification Repr. 2. We support the Dossier submitter´s proposal to classify Thiamethoxam for reproductive toxicity. Results from the two 2-generation studies in rats detected impairment of male fertility in F1 in absence of relevant parental toxicity. Some of the observed effects like testicular lesion (atrophy) were evident already in the low F1 dose groups indicating a high potency. The basis for the maternal NOAEL of 10 ppm in Table 43 is not clear to us especially because no adverse effects were reported in females (in both generations). While there is some uncertainty concerning effects on sperm parameters in the first presented 2-generation study due to methodological issues and absence of a re-investigation of the F1 males, effects on sperms in the second 2-Gen study were detected. Lower sperm counts in testes in F1 rats were observed starting from a low dose, while the amount of the reduction did not display such a clear dose response relationship. At a higher dose also sperm motility was effected. In addition in a 1 year as well as in a 90-day RDT study in dogs decreased testis weights are further indicators of male reproductive toxicity, in the later study accompanied by histopathological changes and reduction in spermatogenesis. Neurodevelopmental effects in rats in terms of reduced absolute brain weights in both sexes and morphological changes at the highest dose were detected. Thiamethoxam affected several parameters related to male reproduction in two species. Therefore we propose at least Repr. 2, H361f, but the possibility to classify as Repr. 1B, H360F should be discussed.				
Dossier Submitter's Response				
The comment on maternal NOAEL is agreed upon (this is a typo in Table 43). There is no maternal toxicity observed in any of the two 2-generation studies.				

As indicated in the CLH report (2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility), FR is of the opinion that since reproductive performances were not impacted Repr. 2 seems more appropriate than Repr.1B. In any case the category will be discussed at RAC meeting.

RAC's response

Thank you for your comments.
RAC agreed on classification in Category 2; H361fd mainly based on testicular tubular atrophy / germ cell loss/disorganization in F1 rats (2-generation studies), ovarian atrophy in mice (90-day study) and effects on brain morphometry/weight in the rat developmental neurotoxicity study. The slight increase in testicular tubular atrophy in the 1-year dog study provides additional support for classification.
Testicular atrophy in the first 2-generation study (1998) is considered to be increased from 1000 ppm, although the dose-response relationship is not very clear. As to the reduced sperm count in the second 2-generation study (2004), it did not show any dose-response relationship (no reduction from 50 to 2500 ppm) and remained more or less within background variability. Thus, it is questionable whether it is treatment-related.
Reduced spermatogenesis observed in young dogs in the 90-day study is considered to reflect a developmental delay rather than direct testicular toxicity (althought a slight contribution of direct testicular toxicity is not excluded).

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Spain		MemberState	7

Comment received

Fertility

The effects on postnatal reproductive development observed in rat offspring (testicular atrophy, decreased sperm cells and delayed balano-preputial separation observed in F1 generation) seems effects on development since fertility and reproductive performance were not impacted by treatment with thiamethoxam. Besides, the decrease on sperm cells in F1 males observed in one of the 2-generation study was not clear dose dependent. Therefore, in the Spanish CA opinion, thiamethoxan doesn´t warrant classification regarding fertility.

Development

In both rat and rabbit developmental toxicity studies reduced foetal weight and delayed ossification were observed only at maternally toxic dose levels.

In the DNT study brain effects were observed in offspring at the highest dose level in the presence of moderate maternal toxicity. The dossier submitter considers that there is an increased qualitative susceptibility of developing organism. However, most of the changes observed in brain morphometric measurements were within the range of historical control provided.

Effects on reproductive postnatal development were also observed in males in the two multigeneration studies. The reproductive effects in F1 males (increased incidence of testicular tubular atrophy in first study and sperm abnormalities in the second one) were noted at dose levels with no concurrent parental toxicity. However, the decrease on sperm cells in F1 males observed in one of the 2-generation study was not clear dose dependent.

Others effects were delayed male puberty in rat progeny was observed in the 2-generation study and in the DNT study and reduction in pup bodyweight observed during late lactation in the 2-generation studies at high dose levels.

The comparison of data with the corresponding classification criteria is not trivial. Data are some kind of borderline and the criteria leave a margin for different interpretations. On overall, the Spanish CA considers that thiamethoxam warrants classification regarding developmetal effects as Repr.2 H361d

Dossier Submitter's Response

Noted. DS considers that effects on fertility cannot be dismissed and trigger classification as reported in the CLH report (2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility).

RAC's response

Thank you for your comments. RAC discussed whether no classification or Category 2 is more appropriate and agreed on classification with Repr. 2; H361fd.
Testicular atrophy in F1 rats can be considered an effect on both fertility and development. Classification for fertility is further supported by ovarian atrophy in the 90-day mouse study and an increase (albeit slight) in testicular atrophy in the 1-year dog study. The changes in brain morphometry were not large (more or less within HCD range) but probably treatment-related and not explained by body weight reductions.

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2019	United Kingdom	Syngenta	Company-Manufacturer	8

Comment received

Syngenta disagrees with the proposal for classification for this endpoint, for the following reasons:
In the rat, a very low incidence of minor testicular atrophy is seen, which is of no functional consequence in terms of sperm production or reproductive function; hence is considered to be non-adverse.
In the dog repeat dose studies, lower testicular weight and immature histological appearance are secondary to general systemic toxicity.
In the rat developmental neurotoxicity study, effects on brain weight, brain morphometric measurements and generalised developmental delay are secondary to lower body weights in treated groups.
See detailed Public Comments, attached as 3 separate documents.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2019-03-20 Thiamethoxam RAC Public Comments.zip

Dossier Submitter's Response

Noted.
It is acknowledged that no impact is observed in reproductive performances in rats. However, in both 2-generation studies in rat, testicular effects were observed in the F1 males in the absence of general toxicity (testicular atrophy in the first study and decreased sperm cells in the second one). At the top dose, in presence of slight general toxicity, delayed preputial separation, increased incidence of germ cell loss/disorganization, Sertoli cell vacuolation and decreased sperm velocity parameters were also observed in F1 males. Tubular atrophy in testis was also observed in the 90-d and 1-year dog studies in the presence of slight general toxicity.

Therefore, classification is considered warranted for fertility.
As it is unclear whether effects on postnatal reproductive development in rat should be considered as effects on fertility or development, no specification (f or d) is proposed.

As reported in the CLH report (2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development), FR is of the opinion that classification for developmental toxicity is also warranted. There is evidence of increased qualitative susceptibility of developing organisms in the multigeneration studies (i.e.: effects on male post-natal reproductive development in the absence of maternal toxicity) and in the developmental neurotoxicity study (effects on brain weight and morphometric changes in the presence of slight maternal toxicity).
As regard, neurotoxic effects vs effects on body weights in the DNT study since brain weight is relatively insensitive to body weight change, the decreased absolute brain weight observed on Day 12 and Day 63 cannot be disregarded as only secondary to decreased bodyweight. Syngenta considers that changes in brain morphometry measurements in high dose male and female F1 offspring were not evidence of developmental neurotoxicity but rather secondary to decreased body weight (general toxicity). However, it is questionable that such body weight reduction (less than 10%) would be responsible of the quite large brain morphometric changes observed at termination in high dose animals. The morphological changes were not associated with neuro-histopathological finding or change in functional or neurobehavioral parameters. However, it should be noted that the Y-maze for learning and memory assessment is a low sensitivity assay of behavioural change unless associated with appropriate difficulty tasks, which was not the case in the present study. Moreover, at termination the same neuroanatomic regions were affected for both males and females (i.e.: dorsal cortex, thalamus and hippocampus) and the morphometric changes went in the same direction (consistent pattern of decreased morphometric measurements).
Furthermore, neuroanatomic location makes biological sense. Indeed, thiamethoxam is a neonicotinoid with pesticidal mode of action based on nicotinic acetylcholine receptor (nAChR) agonist property. The nAChRs are expressed in several brain structures such as cerebellum, hippocampus, entorhinal cortex, basal ganglia and thalamus (Court et al., 2000). Moreover, α4β2 nAChR (high expression of α4 subunit in human foetal brain) is believed to play a morphogenic role during central nervous system development, while α7 nAChR subtype is believed to regulate neuronal growth, differentiation, synaptogenesis during brain development (EFSA Journal 2013;11(12):3471).
Thiamethoxam as other neonicotinoids has weak affinity for mammalian nAChRs and strong affinity for insect nAChRs. However, metabolism of thiamethoxam could give rise to compounds showing higher affinity for mammalian nAChRs. For example, reduction of thiamethoxam to nitrosoguanidine and aminoguanidine derivatives increases potency at the mammalian α4β2 receptor (Kanne et al., 2005). Furthermore, regulatory studies showed that while rapidly eliminated thiamethoxam was able to cross the blood brain barrier (see ADME studies). This is supported by open literature, where thiamethoxam and some of its metabolites were found in the mouse brain after intra-peritoneal administration of 20 mg/kg of thiamethoxam (Ford and Casida, 2006).
Based on those elements, DS is of the opinion that a direct neurotoxic effect cannot be dismissed.

Court JA, Martin-Ruis C, Graham A and Perry E, 2000. Nicotinic receptors in human brain: topography and pathology. J Chem Neuroanat. 2000, 20, 281–298
EFSA, 2013. Scientific Opinion on the developmental neurotoxicity potential of acetamiprid and imidacloprid. EFSA Journal 2013;11(12):3471
Kanne DB, Dick RA, Tomizawa M and Casida JE. Neonicotinoid Nitroguanidine Insecticide Metabolites: Synthesis and Nicotinic Receptor Potency of Guanidines, Aminoguanidines, and Their Derivatives. Chem Res Toxicol, 2005, 18, 1479-1484

Ford KA and Casida JE. Chloropyridinyl neonicotinoid insecticides: diverse molecular substituents contribute to facile metabolism in mice. Chem Res Toxicol, 2006, 19, 944-951

RAC's response

Thank you for your detailed comments.
RAC discussed whether no classification or Category 2 is more appropriate and agreed on classification with Repr. 2; H361fd mainly based on three effects: (1) testicular tubular atrophy / germ cell loss/disorganization in F1 rats in the 2-generation studies, (2) ovarian atrophy in the 90-day mouse study, and (3) reduced size of certain brain regions in the developmental neurotoxicity study.
Although the testicular tubular atrophy in F1 rats was of low severity, together with the ovarian atrophy in mice it is considered sufficient to trigger classification for sexual function and fertility. Additional support for sexual function and fertility classification is provided by the increase (albeit slight) in testicular atrophy in the 1-year dog study. RAC agrees that the effects on reproductive organs in the 90-day dog study represent mainly a developmental delay.
As to the brain weights in the DNT study, we appreciate your analysis and agree that the brain weight reductions on PND 12 can be attributed to reduced body weights. However, a relationship between reduced body weights and changes in brain morphometry on PND 63 has not been demonstrated. The test used to investigate learning and memory (water Y-maze) is generally not very sensitive.

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2019	Netherlands		MemberState	9

Comment received

Sexual function and fertility
Fertility and reproductive performance was not impacted by thiamethoxam. However, in dogs (OECD409/452) tubular atrophy in testis, reduced spermatogenesis and presence of spermatic giant cells was observed in the 90-day and/or 1-year study with no severe general toxicity. In addition, in the F1 generation (two OECD416 rat studies) testicular tubular atrophy, a reduced number of sperm cells (germ cell loss/disorganization and Sertoli cell vacuolation), reduced sperm velocity and delayed balano-preputial separation were observed in the absence of overt general toxicity. These effects are considered adverse alteration to the reproductive system, but as no effect on fertility and reproductive performance was demonstrated and also general toxicity was observed in the males at these dose levels, we agree that thiamethoxam needs to be classified as Repr. 2.
The top dose applied to the females in both 2-generation studies could be considered as too low as this dose level was concluded to be the NOAEL.
Therefore, based on these studies, an effect on the female reproductive function cannot be excluded.

Developmental
OECD414; At 750 mg/kg bw mean foetal bodyweights were significantly lower than controls. At the same dose level, delayed ossification was observed resulting in increased incidence of asymmetrically shaped sternebra 6 and irregular ossification of the occipital bone increased incidence of poor ossification of sternebra 5, absent ossification of metatarsal 1, shortened rib 13, absent ossification of the proximal phalanx of anterior digits 2 & 5, poor or absent ossification of the distal or proximal phalanx of posterior digits 1 – 5. A decreased bodyweight was seen associated with decreased food consumption. These observations are not sufficient to warrant classification.

In the OECD414 rabbit fetal toxicity included reduced fetal weights, an increase in post-implantation loss, delayed ossification and increased incidence of skeletal anomalies and variation, but this was accompanied with severe maternal toxicity.
In the neurodevelopmental study a reduced absolute brain weight and morphometric changes in males and females (same neuroanatomic regions / morphometric changes in the same direction) was observed, but no changes in functional or neurobehavioral were observed (due to insensitivity of the test).
The effects in the two OECD416 rat studies demonstrated effects on reproductive postnatal development (see ad fertility).

The NL CA agrees with the 'classification Repr. 2 H361 with no specification for fertility or development' for adverse effects on sexual function and fertility & development and agrees with the 'no classification' for adverse effects on/via lactation.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Thank you for your comments.
RAC agrees that classification with Repr. 2 is warranted, mainly based on testicular findings in F1 rats, ovarian atrophy in the 90-day mouse study and effects on brain morphometry/weight in the DNT study. The findings in the 90-day dog study are considered to represent a developmental delay rather than direct toxicity to reproductive organs. However, the testicular findings (albeit slight) in the 1-year dog study do provide additional support for classification.
RAC discussed whether 'f' and 'd' should be specified or not and agreed that it is better to specify this. Thus, the RAC proposal is Repr. 2; H361fd.
RAC agrees that the top dose in the 2-generation studies was too low with regard to females, with the implication that female sexual function and fertility has not been sufficiently investigated. This is stated in the RAC opinion.
RAC agrees with no classification for lactation.

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Belgium		MemberState	10

Comment received

Testes and ovaries were impacted in several reliable studies.

In the 2-generation reproductive toxicity study in rats (OECD TG 416) (anonymous 1998 or 1981 ? see editorial comment), testes weight was significantly lower at 158 mg/kg bw/d in F1. Furthermore, same effect was noted in the 90-day oral toxicity study in dogs exposed to 54.8 mg/kg bw/d (OECD TG 409) (anonymous 1996 or 1981? See editorial comment) and in the 1-year oral toxicity study in dogs exposed to 42.0 mg/kg bw/d (OECD TG 452) (anonymous 1998 or 1981? See editorial comment). In these 3 studies, tubular atrophy was observed at low doses (1.8 mg/kg bw/d for the F1 generation of 2-generation study, 54.8 mg/kg bw/d for 90-day study and 21.0 mg/kg bw/d for 1-y study). The incidence of the seminiferous tubular atrophy is even going so far as 70% in the 2-generation reproductive toxicity study.

In the second 2-generation reproductive toxicity study (anonymous 2001 or 2004?, see editorial comment), performed in rats (OECD TG 416), absolute testes weight was significantly higher in the F1 at the 2 highest doses (61.7 and 155.6 mg/kg bw/d) while absolute epididymis weight was significantly higher in the F1 at the highest dose level.

Furthermore, study revealed an increased incidence of germ cell loss/disorganisation +/- Sertoli cell vacuolation in the F1 at 155.6 mg/kg bw/d (5/40, 5/40, 3/40, 7/40 and 20/40). The number of sperm per testis was also significantly affected (87, 93, 70**, 63** and 74* million respectively at 0, 1.2, 3, 61.7 and 155.6 mg/kg bw/d).

In the 90-d repeated dose toxicity performed in dogs (anonymous 1981 or 1996, see editorial comment), a minimal to marked reduction in spermatogenesis and a higher incidence of spermatic giant cells was observed in the testes of all males exposed to the highest dose (54.8 mg/kg bw/d).

Moreover, a developmental neurotoxicity study (OECD TG 426) (anonymous 2003 and 2006 or 1996b, see editorial comment), performed in rats, revealed a significant delay in preputial separation (44.9, 45.6, 45.1 and 46.4**d respectively at 0, 4.3, 34.5 and 298.7 mg/kg bw/d). Although the difference was not significant, a slight delayed preputial separation was noted in the second 2-gen study (47.7, 47.3, 47.2, 46.7 and 48.7d respectively at 0, 1.2, 3, 61.7 and 155.6 mg/kg bw/d).

In addition to the reproductive effects observed in males in the 90-d repeated dose toxicity study performed in dogs (anonymous 1981 or 1996, see editorial comment), females were also affected. Absolute ovaries weight was significantly lower at 50.5 mg/kg bw/d. Furthermore, an immature stage of ovarian development occurred in 3 females out of 4 at the highest dose (50.5 mg/kg bw/d) and an immature stage of uterus development occurred in 2 of these animals.

A 90-days range finding toxicity study (anonymous 1996a), performed in mice, revealed effects in ovaries. Their weight was lower at the 2 highest doses (48.10, 50.07, 41.26, 43.21, 38.71, 31.64** mg respectively at 0, 1.41, 14.3, 176, 543, 1335 mg/kg bw/d). Microscopic examination revealed also an increased incidence of atrophy in the form of reduced number of corpora lutea (0, 0, 1, 1, 5 and 10 females (10 females examined per group), respectively at 0, 1.41, 14.3, 176, 543, 1335 mg/kg bw/d).

BE CA wants to point out that all these effects were observed at low dose and in several species (rats, mice and dogs). Furthermore, these effects were observed in the absence of other toxic effects.

Taking into account the previous arguments, BE CA is of the opinion that a classification as Repr. 1B should be discussed.

Editorial comment :
There are important differences in the reference of studies presented in the section 2.6.6 Summary of reproductive toxicity (equivalent to section 10.10 of the CLH report) :

In table 43 (page 74) : 2-generation reproduction study (anonymous, 1998, vol3CA B.6.6.1.1). In the table, DS mentioned a paternal NOAEL of 1000 ppm and a maternal NOAEL of 10 ppm. However, no maternal effect was observed in all doses level, then the NOAEL is not 10 ppm but of 2500 ppm. Moreover, in the chapter 2.6.6.1.1, the reference of the first 2-generation study (page 78) was 1981 not 1998 as in the table 43.

In table 43 (page 75) : 2-generation reproduction study (anonymous, 2004, vol3CA B.6.6.1.2). While, in the chapter 2.6.6.1.1, the reference of the second 2-generation reproductive toxicity (page 82) study was 2001, not 2004.

In table 43 (page 75) : developmental neurotoxicity study in rat (anonymous 2003 and

2006, Vol3CA B.6.7.1.3). While, in the chapter 2.6.6.1.1, the reference of the developmental neurotoxicity study (page 91 in a table) was 1996 not 2003 and 2006.

In table 43 : 90-day oral toxicity study in dog (anonymous, 1996, vol3CA B.6.3.2). While, in the chapter 2.6.6.1.1, the reference of the guideline 90-day dog study was 1981 not 1996.

In table 43 : 1-year oral toxicity study in dog (anonymous, 1998, vol3CA B.6.3.3). While, in the chapter 2.6.6.1.1, the reference of the 1-year dog toxicity study was 1981 not 1998.

In page 92, it's mentioned that "In repeat dose studies in rat and mice, no effect on reproductive organs was observed". However, in the 90-days range finding oral toxicity study (anonymous 1996a), performed in mice, effects in ovaries were observed (organ weight and microscopic changes).

Dossier Submitter's Response

- The comment on maternal NOAEL is agreed upon (This is a typo in Table 43). There is no maternal toxicity observed in any of the two 2-generation studies.
- It is acknowledged that effects on ovary were observed in the mice 90-d (decreased weight, atrophy and reduced numbers of corpora were observed from 3500ppm (626 mg/kg bw/d) onwards with concomitant general toxicity. Such effects were not observed in the 18-month study up to 2500ppm (479 mg/kg bw/d).
- As indicated in the CLH report (2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility), FR is of the opinion that since reproductive performances were not impacted Repr. 2 seems more appropriate than Repr.1B. In any case the category will be discussed at RAC meeting.

- Editorial comments:

Dates in Table 43 are related to the year the studies were performed while in the text the dates precise the version of the followed OECD TG.
The first 2-generation was performed in 1998 according to OECD TG 416 (1981) while the second 2-generation study was performed in 2003 according to the updated OECD TG 416 (2001) including more sensitive end-points.
Same answer for the dog studies performed in 1996 and 1998 for the 90-day and the 1-year studies respectively according to OECD TG 409 (1981) and OECD TG 452 (1981) respectively.
As regard the DNT study, it is agreed that there is a typo in table page 91; the reference should be 2003, 2006 and not 1996.
The study was performed in 2003 with addenda in 2006 and 2007 according to OECD 426 (2003 draft).

RAC's response

Thank you for your comments. RAC has discussed all these effects and concluded that Category 2 for sexual function and fertility is appropriate mainly based on the testicular atrophy / germ cell loss/disorganization in the 2-generation studies and ovarian atrophy in the 90-day mouse study. It should be noted that the severity of testicular tubular atrophy in rats was mostly low and a more marked ovarian atrophy in mice was only observed at a relatively high dose (above 1000 mg/kg bw/d).
As to the 90-day study in dogs, RAC is of the view that the immature ovaries and uterus can be fully explained by a general developmental delay due to severe toxicity (body weight gain 0.5 kg vs 2.9 kg in the control, animals were around the age of reaching

sexual maturity at the end of the study). The findings in top dose male dogs in the 90-day study are also likely to be a result of a developmental delay rather than of direct testicular toxicity given the results of the 1-year study where only a weak increase in testicular atrophy was observed.
Overall, the available data are considered not sufficient for classification in Category 1B as the relevant findings were mainly of low severity and reproductive performance was not affected. Saying this, RAC acknowledges that the potential of the substance to adversely affect female sexual function and fertility has not been sufficiently investigated due to low dosing in the 2-generation studies (no general toxicity in females, higher doses would have been tolerated).

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Spain		MemberState	11
Comment received				
The lowest LD50 value in male mice was 783 mg/kg bw and 964 mg/kg bw in female mice. As both LD50 values are within the range 300-2000 mg/kg bw, thiametoxam should be classified as Acute Tox 4, H302 "Harmful if swallowed". Therefore, based on the results of the acute toxicity studies in rat and mouse and in accordance with CLP criteria, Acute tox 4 (H302) should be confirmed and the asterix should be removed in the current entry. A harmonised ATE value is also proposed to facilitate consistent classification of mixtures containing thiamethoxam. Taking these data into account, the Spanish CA also support the ATE of 800 mg/kg bw for acute oral toxicity.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you, RAC agrees with Acute Tox. 4 but prefers rounding of the lowest LD50 (783 mg/kg bw) to two significant figures for the purpose of ATE setting, i.e. to 780 mg/kg bw/d.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Belgium		MemberState	12
Comment received				
The classification for thiamethoxam for Acute Tox. 4, H302, is supported, however an ATE of 783 mg/kg bw should be considered. In the acute toxicity study performed in mice (anonymous, 1996a), following OECD TG 401, the estimated LD50 was 783 mg/kg bw in males and 964 mg/kg bw in females. These results were supported by the acute toxicity study performed in rats (anonymous, 1996) which revealed a LD50 of 1563 mg/kg bw in both sexes. BE CA is of the opinion that the lowest LD50 recorded in a valid acute toxicity study should be taken as the ATE. Based on this, BE CA considered that an ATE of 783 mg/kg bw should be warranted.				

Dossier Submitter's Response
To facilitate classification of mixtures, DS has proposed a rounded value of 800 mg/kg bw.
RAC's response
Thank you for your comment. RAC agrees with Acute Tox. 4. Rounding is considered acceptable as rounded values are easier to use and unrounded values may give an impression of precision that in fact does not exist (the 95% confidence interval for the LD50 in male mice is 619 – 1000 mg/kg bw). However, RAC proposes to round the LD50 to two significant figures for the purpose of ATE setting, i.e. to 780 mg/kg bw.

Date	Country	Organisation	Type of Organisation	Comment number
11.03.2019	Denmark		MemberState	13
Comment received				
DK agrees on the proposed classification: Acute toxicity 4 - H302 Harmful if swallowed. ATE value: 800 mg/kg bw.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you, please see response to comment no. 11.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
11.03.2019	Denmark		MemberState	14
Comment received				
-				
Dossier Submitter's Response				
RAC's response				
-				

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	Germany		MemberState	15
Comment received				
2.8 Fate and Behaviour in the environment: We agree with the conclusion to classify thiamethoxam as "not ready biodegradable". Nevertheless, we want to point out that in the substance approval under the biocidal product regulation further information is available regarding degradation in soil and in water/sediment systems, which should be taken into account. This applies especially to the biodegradation behaviour in water/sediment systems since the CLH-report identifies a data gap for this endpoint.				
Dossier Submitter's Response				
Thank you for your comment. This CLH-report has been based on the data submitted in the frame of the EU PPP renewal dossier for thiamethoxam. Since reliable data are already available from PPP dossier (field dissipation study for soil and aerobic mineralization in dark study for water), the active substance classification would not change.				
RAC's response				
Noted. Available data on degradation have been taken into account.				

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	United Kingdom		MemberState	16
Comment received				
Thiamethoxam (EC: 428-650-4; CAS: 153719-23-4) Ecotoxicity: Chronic toxicity to Chironomus riparius: As analytical verification is limited to treatments above the NOEC, we feel the surrogate approach using acute endpoints in the range 0.01 to 0.1 mg/l (including the most acutely sensitive endpoint and acute toxicity to Chironomus endpoint) should be noted. This supports the Aquatic Chronic 1, M=10 proposal.				
Dossier Submitter's Response				
Noted that the surrogate approach would also support the Aquatic Chronic 1, M=10 proposal.				
RAC's response				
Noted. The surrogate approach would lead to same classification and M-factor as that based on the NOEC.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Finland		MemberState	17
Comment received				
FI CA supports the conclusions that thiamethoxam is not considered as rapidly degradable and unlikely to have a potential for bioaccumulation for the classification purposes. There are toxicity test data available for classification purposes of aquatic hazards from all the trophic levels. According to studies listed, the most sensitive trophic level is invertebrates. The key data for aquatic acute classification was acquired from a non-guideline study using a species of mayfly, Cloeon dipterum. Generally following the OECD TG 202 guideline, the study is considered reliable and appropriate for hazard assessment. The EC50 value determined in the test was 0.014 mg/L. There are also other studies with endpoints in the same range supporting the classification. The lowest aquatic chronic toxicity value was from study performed with midge larvae, Chironomus riparius. According to the chironomid study, the NOEC value was 0.0027 mg/L. The test was considered reliable for hazard assessment despite deviations from the OECD TG 219 and, furthermore, as the test substance was not observed dissipating into the sediment. The NOEC proposed to be used is based on the measured geometric mean. However, the mean measured concentrations declined below the level of detection during the test and the concentrations of the test medium was analysed only three times during the test. FI CA acknowledges that the actual NOEC has been lower than based on nominal concentrations but would welcome further elaboration of the way the NOEC was derived. Based on the available information and the classification criteria, FI CA supports the proposed classification of Aquatic Acute 1, H400 with M-factor of 10 for thiamethoxam.				
Dossier Submitter's Response				
FR agrees that actual NOEC has been lower than based on nominal concentrations and therefore FR expressed the endpoint in term of geomean measured concentrations in water				

based on analytical verification (% of nominal) reported in table 8.2.5.3-1. As commented by UK (see comment number 16), it can be noted that the surrogate approach using acute endpoints in the range 0.01 to 0.1 mg/l (including the most acutely sensitive endpoint and acute toxicity to Chironomus endpoint) would also support the Aquatic Chronic 1, M=10 proposal.
RAC's response
Noted. Nevertheless, the surrogate approach would lead to same classification and M-factor as that based on that NOEC.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Spain		MemberState	18
Comment received				
We agree with the dossier submitter to classify thiametoxam as H228 Flammable solid category1				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
According to the CLP regulation, classification in this hazard class should be based on a result of the UN Test N.1. The EC A.10 test is very similar to the UN Test N.1 except that the A.10 test is unable to distinguish between Category 1 and 2. According to the RAR, the test was conducted twice. First, thiamethoxam was tested strictly following the A.10 method, including the use of a non-combustible base plate (made from glass). The result was negative. The second, "extended" test using a fibreboard base plate was positive. Both the UN Test N.1 and the A.10 test clearly specify that the base plate must be non-combustible. Pyrolysis products from the fibreboard (a wood-based material) are likely to have contributed significantly to the combustion of the test substance in the second test. RAC considers this deviation from the harmonized protocol rather critical and does deem the test using fibreboard suitable for classification purposes. Therefore, RAC proposes no classification for flammable solids based on the negative result obtained in the guideline A.10 test.				

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	Germany		MemberState	19
Comment received				
Review of Flam. Sol. 1; H228 versus Self-reactive properties: Classification as "Self-reactive substances" was not considered for this proposal. Due to the fact that there are chemical groups present in the molecule which are associated with explosive or self-reactive properties this hazard class should be considered within the CLH proposal. Please, cf. screening procedures in Appendix 6 of the UN-MTC, see Tables A6.1 and A6.3 (Reference: UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, Sixth Revised Edition, New York and Geneva: United Nations, 2015, ISBN				

978-92-1-139155-8, ST/SG/AC.10/11/Rev.6.)

Self-reactive substances or mixtures are classified in one of the seven categories of 'types A to G' according to the classification criteria given in Section 2.8.2.3 of Annex I, CLP. According to Section 2.8.4.2 of CLP the classification procedures for self-reactive substances and mixtures need not be applied if:

(a) There are no chemical groups present in the molecule associated with explosive or self-reactive properties. Examples of such groups are given in Tables A6.1 and A6.2 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria (Fifth Revised Edition, 2009); or

(b) For a single organic substance or a homogeneous mixture of organic substances, the estimated SADT for a 50 kg package is greater than 75 °C or the exothermic decomposition energy is less than 300 J/g. The onset temperature and decomposition energy can be estimated using a suitable calorimetric technique (see Part II, sub-section 20.3.3.3 of the UN RTDG, Manual of Tests and Criteria).

However, for Thiamethoxam no such data were presented in the CLH report to be able to conclude on non-classification as a self-reactive substance.
With regard to the test for flammable solids it is likely that the result was misinterpretated due to deflagration properties as reported in the evaluation for explosives, see UN Test 2(c) (i) Time/pressure Test.

When comparing with the CLP criteria it needs to consider that the traditional aspects of explosive properties, such as detonation, deflagration and thermal explosion, are incorporated in the decision logic Figure 2.8.1 "Self-reactive substances and mixtures" of CLP. Consequently, the determination of explosive properties as prescribed in the hazard class explosives needs not to be conducted for self-reactive substances and mixtures.

Furthermore, self-reactive substances and mixtures should not be considered for classification as flammable solids since flammability is an intrinsic hazard in this class. Consequently, the classification criteria of flammable solids need not to be applied for self-reactive substances and mixtures.

To close the data gap for self-reactive substance it should be performed at least the SADT for a 50 kg package. Only, if the SADT for a 50 kg package is greater than 75 °C, Thiamethoxam should be classified as Flammable Solid, Category 1. Otherwise, the classification procedure for self-reactive substances or mixtures shall be performed in accordance with test series A to H as described in Part II of the UN RTDG, Manual of Tests and Criteria.

Dossier Submitter's Response

The notifier submitted a report to clarify this point.
Self-reactive properties are not usually addressed in the formal GLP regulatory safety studies provided by the notifier. However, the notifier has carried out this testing for internal safety purposes. He has an internal study which reports the results of UN Test H.4, showing that the SADT is greater than 75°C. Although the study was carried out in a GLP facility, it was not conducted as a formal GLP study and no claim of GLP compliance is being made for the work. However, the tests were carried out on material obtained from routine manufacture and the results should therefore be considered as representative of TMX as supplied.

UN Test H.4 involves testing the material in a container simulating the heat-loss characteristics of a 50kg package and holding it in an oven at a temperature of 75°C for a period of 7 days. If the sample temperature exceeds the test temperature by 6°C or more at any point during the test, the SADT is considered to be less than or equal to 75°C, otherwise it is considered to be greater than 75°C. In this particular case, the study was carried out in order to address concerns about the storage of the material in warehouses and the test period was extended from 7 to 30 days (i.e. a more rigorous test). No significant exothermic activity was detected, even over this extended period, clearly showing the SADT to be > 75°C. The classification as a self-reactive substance need not be applied if the exothermic decomposition energy is less than 300 J/g ***OR*** the SADT for a 50kg package is greater than 75°C. Although DSC measurements show the exothermic decomposition energy is very much greater than 300 J/g, the fact that the SADT is greater than 75°C means that TMX should not be classified as a self-reactive substance.
RAC's response
Thank you for your comments. Only the hazard class 'flammable solids' was open for public consultation and assessed by RAC. RAC proposes no classification for flammable solids based on a guideline A.10 test (see response to comment no. 18).

PUBLIC ATTACHMENTS
1. 2019-03-20 Thiamethoxam RAC Public Comments.zip [Please refer to comment No. 8]