COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

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Last data extracted on 26.03.2019

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

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.				

Date	Country	Organisation	Type of Organisation	Comment number
11.03.2019	Denmark		MemberState	3

Comment received
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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.				

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: Reproductive toxicant Cat. 2 H361.				

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-Gen 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 d 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 Cat 2 (fertility), but the possibility to classify as 1B should be discussed.				

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 Reproductive toxicant Cat. 2 H361d				

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

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-d and/or 1-y 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 reproductive toxicant Cat 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 Cat 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.

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-d 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-y 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-gen study, 54.8 mg/kg bw/d for 90-d 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).

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.				

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.				

Date	Country	Organisation	Type of Organisation	Comment number
11.03.2019	Denmark		MemberState	13
Comment received				
DK agrees on the proposed classification: Acute toxicity (oral), cat. 4 - H302 Harmful if swallowed. ATE value: 800 mg/kg bw.				

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				
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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.				

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.

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.				

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				

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.

Date	Country	Organisation	Type of Organisation	Comment number
11.03.2019	Denmark		MemberState	20
Comment received				
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PUBLIC ATTACHMENTS
1. 2019-03-20 Thiamethoxam RAC Public Comments.zip [Please refer to comment No. 8]