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.

ECHA accepts no responsibility or liability for the content of this table.

Last data extracted on 26.11.2019

Substance name: Reaction mass of 3-(difluoromethyl)-1-methyl-*N*-[(1RS,4SR,9RS)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]pyrazole-4-carboxamide and 3-(difluoromethyl)-1-methyl-*N*-[(1RS,4SR,9SR)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]pyrazole-4-carboxamide; isopyrazam
CAS number: 881685-58-1
EC number: -
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2019	Germany		MemberState	1
Comment received				
Regarding the solubility in organic solvents under section 7 of the CLH Report and in the document B.2, the solubility in dichloromethane is stated as 303 g/L. During our review, we found different values (303 g/L or 330 g/L) for the solubility in dichloromethane for the same reference. As the study report was not available, we could not check which value is correct. Please clarify.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium		MemberState	2
Comment received				
BE CA would like to thank the UK Competent Authority for the submission of this CLH proposal. Overall, we support the conclusions proposed for all the physical and environmental hazard assessment, as well as STOT SE, skin corrosion and irritation, eye damage, skin sensitisation, and germ cells mutagenicity. However, we do have some comments regarding the carcinogenicity, reproductive toxicity and STOT RE endpoints. Furthermore, we do have an identification issue with this substance. To guarantee a high level of health and environmental safety, BE CA is of the opinion that this CLH proposal should concerns isopyrazam as covered by the ISO name (which means a maximal content of 30% of the "anti" enantiomer) and not as primarily intended by the dossier submitter (e.g. a maximal content of 15% of the "anti" enantiomer); alternately if it is not conceivable, then we believe that two different entries (identification numbers) for each substance must be available in order to ensure a classification for all chemicals. In any case (1 or 2 separate entries), the full band of anti-enantiomers (0-30%) has to be covered by the harmonized classification.				

Date	Country	Organisation	Type of Organisation	Comment number

21.11.2019	Switzerland	Syngenta Crop Protection AG	Company-Manufacturer	3
Comment received				
Syngenta supports the dossier submitter's conclusion on classification for carcinogenicity and disagrees with the dossier submitter's conclusion on classification for reproductive toxicity. Additional information related to hazard classes Carcinogenicity and Reproductive Toxicity is herewith provided. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20191121 CLH submission isopyrazam _Non-confidential.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20191121 CLH submission isopyrazam _Confidential.zip				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2019	Germany		MemberState	4
Comment received				
The involvement of CAR in the mode of action was intensively studied in Annex 2: Mode of action and human health relevance assessment of the increased incidence of liver tumors in the female han wistar rat dosed with isopyrazam. The proposal uses an approach originally developed by IPCS/ILSI (2001). However, concerns about different modes of action for rodent liver tumor formation, e.g. AhR activation by complex HSP90-AhR release from AIP were not addressed in Table 3 of the document. The effects shown are apparently not limited to CAR activation but likely include activation of AhR related pathways. We further consider that there is evidence that for hepatocellular foci/adenoma there is a plausible alternative mode of action with relevance to humans. In addition, in regulatory accepted approaches such as AOP framework and for the possible use in risk assessment, the key event relationships (also used in Fig.1 of the document) have to be proven by weight of evidence analyses. The grades of low, moderate and strong were attributed to empirical support by a number and quality of studies also from open literature. Furthermore, inhibition studies demonstrating essential-ity for key events were not provided. Both empirical support and essentiality were not prov-en for isopyrazamin in the proposed MoA approach. Overall, the proposal of a mode-of-action hypothesis for induction of one possible pathway for liver tumours in rats does not exclude different MoAs as listed in the AOP Wiki database (AOP41: Sustained AhR activation leading to rodent liver tumours; AOP32: Inhibition of iNOS, hepatotoxicity, and regenerative proliferation leading to liver tumors, AOP46: AFB1: Mutagenic mode-of-action leading to hepatocellular carcinoma; etc.) and therefore does not exclude human relevance for these different MoAs as well. Thus, the classification as Carc. 2, H351 rather than non-classification appears more appropriate.				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Switzerland	Federal Food Safety and Veterinary Office	National Authority	5
Comment received				
CH proposes to classify Isopyrazam as Carc. Cat. 2, in line with the argumentation for classification of Sedaxane as Carc. Cat. 2. Especially since the MoA analysis in the CLH report of Sedaxane is partly based on data with Isopyrazam. Isopyrazam and Sedaxane are structural analogs, and both induce treatment-related uterine adenocarcinomas at similar dose levels and comparable incidences. Human relevance of these tumors has to be very carefully analysed, especially in light of the ongoing discussion on a potential risk of SDHIs				

for humans (see e.g. discussions on Pydiflumetofen at the PRAS Meeting in September 2018). As long as the mode of action of SDHIs has not been fully understand elucidated, it is not possible to neglect the human relevance of uterine tumours found after treatment of rats with Isopyrazam and Sedaxane. SDHIs are supposed to lead to tumor formation by inducing epigenetic modifications through the accumulation of succinate (Letouzé et al. 2013), however, in the MoA Analysis for the uterine adenocarcinomas submitted by the applicant, epigenetic modifications were not considered as a potential mode of action for Isopyrazam induced tumours. Therefore, without an established MoA, which does not operate in humans, Isopyrazam should be classified as Carc. 2; H351.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2019	France		MemberState	6

Comment received

FR: Isopyrazam belongs to the chemical family of Succinate DeHydrogenase Inhibitors (SDHI), which rely on the inhibition of the fungal enzyme succinate dehydrogenase (mitochondrial complex II).
As regards the potential mode of action underlying tumours formation, it is noteworthy that a high concern regarding the use of SDHIs as fungicides in agriculture has been raised by researchers and clinicians from French institutes with respect to the carcinogenic potential linked to SDH inhibition (Benit et al, 2018). This is based on human data where genetic mutations of SDH (leading to the loss of activity) are the cause of human diseases:
- cell death (encephalopathies and cardiomyopathies) (Bourgeron et al. 1995 ; Parfait et al. 2000 ; Levitas et al. 2010) or
- uncontrolled proliferation of cells causing cancer (Gimenez et al. 2002, 2003 ; Baysal et al. 2000 ; Burnichon et al. 2010 ; Janeway et al. 2010….). The tumour formation rather results from epigenetics modifications, which have been shown to be a long-term consequence of succinate accumulation, acting as an oncometabolite (Letouze et al. 2013).
A report from an expert group set up by ANSES as well as the ANSES opinion published in January 2019 are available on line:
https://www.anses.fr/fr/system/files/PHYTO2018SA0113Ra.pdf
ANSES has informed EFSA, ECHA, DG Health and Food Safety and Competent Authorities about this raised concern.

Increased incidences of hepatocellular and uterine tumours were observed in the rat carcinogenicity study with isopyrazam.

Liver tumours:
The proposed mode of action (MoA) for the increased incidence of liver tumours, involving the activation of CAR, could be considered plausible. Nevertheless, it is considered that uncertainties remain as some data are missing to substantiate this MoA (e.g. neither in vitro CAR/PXR assay nor data on gene expression were available, no CAR-Knock-Out animals were used…). Furthermore, it is noted that the data available to exclude the human relevance (if the postulated MoA would have been accepted) could be considered insufficient as only one donor was used in the study using human hepatocytes (in line with RAC opinion on Sedaxane (March 2019), a structurally related active substance of the same pesticide class (SDHI)).

Uterine tumours:
The postulated MoA for the increased incidence of uterine carcinomas is not considered sufficiently substantiated by the available data, with high uncertainties regarding several key events.
It is noted that nearly the same MoA was proposed for sedaxane, a structurally related active substance of the same pesticide class (SDHI) showing the same type of tumours. The

18-month carcinogenicity study conducted on isopyrazam was submitted during the harmonised classification and labelling process for sedaxane and considered by FR as Dossier Submitter during the commenting phase (see RAC opinion March 2019 and its Annex 2).
In addition to the general uncertainties related to the postulated MoA discussed by RAC in the context of sedaxane assessment, the specific uncertainties highlighted by FR for isopyrazam are the following:

* Key event three: Suppression of age-related decrease in dopaminergic signalling
- At the dose level of 3000 ppm, the mean dopamine concentrations in the median eminence of the hypothalamus were only statistically significantly higher at Week 26, and were not affected later (at week 52, week 66 and week 80).
- The measure of dopamine turnover in the median eminence was unaffected by treatment.
- Across the time points in this study, the concentration of dopamine and DOPAC in the median eminence remained fairly constant in the control animals from week 26 through week 80.
- According to the study report and Annex 3 of the CLH report (3.2.7), there was no difference in the amount of tyrosine hydroxylase staining in the arcuate nucleus by immunohistochemistry (for protein) or in situ hybridization (for RNA) between control and test substance-treated groups at week 52. There were also no test substance-related differences in the number of tyrosine hydroxylase-positive (dopaminergic) neurons in the arcuate nucleus between control and treated groups by unbiased stereology at weeks 66 and 80.
Therefore, these results do not support a decreased of dopamine with time (up to 80 weeks) in the control animals and a preservation of the dopaminergic activity with isopyrazam treatment, as postulated.

* Key events five and six: altered transition to reproductive senescence, increased total number of oestrus cycles and proliferation
- The 18-month isopyrazam study seems to suggest that the high dose level of 3000 ppm can delay the time of reproductive senescence onset. It is however noteworthy that in the GLP statement of the study report, it is mentioned that the systems used for calculation and tabulation of estrous cycle data were not validated.
- There were no apparent test substance-related effects (no dose response and/or no time-relationship) on proliferative lesions in the uterus, cervix and vagina in the 18-month isopyrazam study or in the 2-year rat study which is not in accordance with a proliferation process, as suggested.

In conclusion, FR is of the opinion that the experimental data do not provide enough evidence to support the postulated MoA of rat uterine tumours induced by isopyrazam. Furthermore, an alternative MoA through SDH inhibition and accumulation of succinate (considered as oncometabolite) could not be ruled out (see above).

As a conclusion, it is considered that classification of isopyrazam as Carc 2 is warranted based on uterine and liver tumours observed in rats.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium		MemberState	7
Comment received				
In rats, in a 2-year chronic toxicity and carcinogenicity study (anonymous 2008a and anonymous 2009), an increase in liver adenoma (1.9, 0, 0, 5.8%in males and 0, 1.9, 1.9, 21.15% in females at 0, 100, 500 and 3000 ppm respectively) was observed. Contemporary HCD (2007-2009) in females show a rate of 0-1.9 % adenomas, but these HCD are				

extracted from only 3 studies and should be taken with caution.

Also, an increase in the incidence of uterus carcinomas was reported with 1.9, 3.8, 5.8, and 28.8% of affected females at 0, 100, 500 and 3000 ppm (=0, 7, 35 and 233 mg/kg bw/d), respectively. The same remark as above is valid for the HCD (1.9-7.8 %). The incidence of carcinomas in relatively high considering the exposure levels. As only one study in available in rats, the consistency of this effect could unfortunately not be assessed.

In mice, in an 80-week carcinogenicity study (anonymous 2008b), no neoplastic findings were reported.

Nonetheless, BE CA would like to express its concerns regarding all the justification data provided by the dossier submitter. Could the induction of CYP be caused as an adaptative response of the liver, the target organ of Isopyrazam? Should we not maintain some reserves on the mode of action behind these carcinogenic effects? Are all uncertainties clarified?

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Switzerland	Syngenta Crop Protection AG	Company-Manufacturer	8

Comment received

Agree with the dossier submitter's conclusion on classification for carcinogenicity.
The available data support the conclusion that isopyrazam does not pose a carcinogenic hazard to humans. Whilst administration of isopyrazam at dietary concentrations of 3000 ppm for 24 months to female Han Wistar rats resulted in higher incidences of hepatocellular adenomas and uterine adenocarcinoma, extensive MoA studies demonstrate that these are not relevant to humans. Sustained deficits in bodyweight gain were observed in females at 3000 ppm, which was approximately four-fold the recommended maximum tolerated dose (MTD).
The available data for isopyrazam support the proposed MoA and key events in rats and is well-described in the scientific literature. A sustained reduction in food utilization, reduced adipose tissue and leptin, affecting the hypothalamic feedback mechanisms, delaying age-related reductions in tuberoinfundibular dopaminergic (TIDA) neurons, which manifests as a reduction in prolactin, delaying reproductive senescence. The proportional increase in rats in persistent estrus lead to an increase in rats with elevated estrogen:progesterone ratios at the top dose, enhancing the proliferative stimulus to the uterine endometrium, resulting in an increase in spontaneous lesions in this tissue. Lower plasma levels of prolactin, led to reduced proliferative stimulus on the mammary and anterior pituitary glands, resulting in a reduction in tumour incidence. Thus, the shift in tumour incidence is dependent on a marked and sustained deficit in bodyweight gain, which was observed in female Han Wistar rats receiving 3000 ppm isopyrazam.
The applicant believes that the MoA assessment provides robust evidence of all key events, either directly or via associative events. Whilst steroid hormone levels were not specifically measured, oestrous cyclicity was considered a pragmatic and appropriate marker of the oestrogen:progesterone ratio given the significant technical and ethical challenges in female hormone measurement. Inherent intra- and inter- animal variability in estrogen and progesterone levels throughout the estrous cycle would have necessitated significantly larger groups, in order to sufficiently power the parameters. Furthermore, measurement of estrogen and progesterone would not have provided information on the key events regarding target tissues. No further data is considered necessary to support the MoA for uterine tumours.
Given the physiological control of the female reproductive cycle, and the drivers for

reproductive senescence in humans are fundamentally different from those that occur in the rat, the MoA is not considered relevant to humans. Thus, the available data support the conclusion that the marginal increase in uterine tumours in isopyrazam treated rats does not pose a carcinogenic hazard to humans.
The available data for isopyrazam support a proposed MoA in female rats involving activation of the constitutive androstane receptor (CAR), leading to an early, transient, increase in hepatocellular proliferation and hepatocellular foci, which progress to form liver tumours. Contrary to rats, treatment of primary human hepatocytes (n=3) with isopyrazam had no effect on hepatocellular proliferation when tested up to the limit of cell viability. This pattern of effects matches the known species differences that have been demonstrated for other CAR activators, and the weight of evidence indicates that it represents a qualitative difference in the established MoA for isopyrazam between rats and humans. Numerous CAR knockout (KO) mice studies have been conducted to demonstrate this MoA for model compounds, which has been successfully demonstrated via alternative in vitro methods. Consequently, no further data is considered ethically or scientifically justified to support the MoA for liver tumours. Thus, the available data demonstrates that this MoA is not relevant to humans and classification is not appropriate.
Isopyrazam – Human Relevance Framework Assessment of Liver Tumour Induction in Female Rats attached to support the above statement.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20191121 CLH submission isopyrazam _Non-confidential.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20191121 CLH submission isopyrazam _Confidential.zip

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2019	France		MemberState	9
Comment received				

FR :

Page 60:
- Delayed preputial separation and vaginal opening were considered by the DS to be secondary to reduced body weight gains and subsequent lower post-weaning body weights. Nevertheless, this statement should be substantiated by the available data (e.g. tabulated results including mean and range of the age and body weights at sexual maturation, historical control data…).
- Decreased number of implantation sites and decreased mean litter size at birth were statistically significant at the high dose level in both generation. As only 2 studies are available for historical control data (HCD), it is more appropriate to consider concurrent control group rather than HCD.

Page 76:
The classification of isopyrazam Repr 1B H360D as proposed by the DS is supported, based on the consistent effects on the eyes observed in the offspring in 2 strains of rabbits in the 4 available studies.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium		MemberState	10
Comment received				

Fertility
In an OECD 416 study performed on rats, at the highest dose of 3000 ppm, the total litter size was significantly decreased for both the F1 (-13%*) and F2 (-12%*) generations, in comparison with the controls; the number of implantation sites in the F0 and F1 mothers were also significantly decreased (12.3 v.s. 10.7* and 12.8 v.s. 11.4*, in controls and F0 then F1 mothers, respectively) compared to controls. Concerning the historical control data (HCD), we acknowledge they are contemporary to the actual study, but we would like to highlight the fact that only a very limited number of studies was used to create these HCD (only 2) and therefore their relevance might be discussed. Considering these effects appear at a relatively low dose (close to 300 mg/kg bw/d), in two generations, we are of the opinion that these effects matter for classification of fertility and would like the dossier submitter to consider a Repr. 2; H361 classification for this endpoint.

Developmental toxicity
In an OCED 414 in rats (Isopyrazam 93:7), at 250 mg/kg bw/d, an increase in post-implantation loss and in the incidence of incomplete ossification of several foetal bones (cervical centra (5.6 – 35.7%**), sternum (12.4%**), caudal arches (4 – 8%), hind-paw bones (17%**) and fore-paw bones (8%**)) was reported as well as a decrease in mean foetal body weight. This was correlated with maternal effects such as a decrease in body weight gain.

In another OECD 414 study in rats (Isopyrazam 70:30), at 200 mg/kg bw/d, a decrease in mean foetal body weight and an increase in foetal visceral variations (50% v.s. 35% in controls) as well as in the incidence of non-ossification in several bones (vertebral centra and hind limbs phalanges) were reported. In mothers, at the same dose level, body weight gain was reduced and sedation was observed in all females when the study started. At 75 mg/kg bw/d, while body weight gain was reduced in mothers, the foetal mean body weight was also decreased (-6 % **, in comparison with the controls) and non-ossification was observed in one vertebral centrum.

In rabbits, three dose-range finding studies and one OECD 414 are available. Consistency was noted between the studies with reduced size of the eye (observed in Anonymous 2008b at 400 mg/kg bw/d without any maternal toxicity as "slightly reduced eye size", in Anonymous 2008c at 600, 800 and 1000 mg/kg bw/d without any maternal toxicity as "small eyes (malformations)" or "slightly small eye (variations)" or microphtalmia, in Anonymous 2008a at 700 and 1000 mg/kg bw/d as "eye malformation" but in presence of maternal toxicity such as decreased BW-gain and FC, decreased faeces production, increased GGT, increased relative liver weight, hepatocellular hypertrophy, and centrilobular hepatocellular vacuolation; and finally in Anonymous 2008b at 500 mg/kg bw/d as microphtalmia in presence of maternal toxicity noted as decreased faeces production, decreased FC, increased absolute liver weight, hepatocellular hypertrophy, and centrilobular hepatocellular vacuolation).

On the basis of the severe adverse effects seen not only in the rabbit (microphtalmia) but also in the rat (non-ossification) plus, not necessarily reported in presence of maternal toxicity, at doses relatively low (starting at 75 mg/kg bw/d in the rat and at 400 mg/kg bw/d in the rabbit), BE CA supports the proposal to classify Isopyrazam as Repr. 1B; H360.

In conclusion, we would be in favour of a Repr. 1B; H360Df for Isopyrazam.

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Switzerland	Syngenta Crop	Company-Manufacturer	11

		Protection AG		
Comment received				
Disagree with the dossier submitter's conclusion on classification for reproductive toxicity. There is no evidence that isopyrazam causes adverse effects on sexual function, fertility or development in the rat. The only finding of relevance to classification for reproductive toxicity is the observation of microphthalmia and small eyes at high dose levels in the rabbit (≥600 mg/kg/day). Microphthalmia was only observed in the presence of marked maternal toxicity and is considered likely to be due to a non-specific secondary mechanism of disturbed homeostasis. Rabbit studies on isopyrazam were performed by two separate contract research organizations (CRO). Outsourced during the closure of the Central Toxicology Laboratory (CTL, Alderley Park, UK), the isopyrazam rabbit prenatal developmental toxicity studies were some of the first externally managed studies conducted for Syngenta. At RCC (Füllinsdorf, Switzerland), two preliminary studies in Himalayan rabbit reported foetal findings of small eyes, which were not sufficient to be described as microphthalmia. Small eyes had not previously been described by RCC and were not in the laboratory's glossary of foetal effects. Consequently, there were uncertainties in the procedures in place for minimising bias and reporting at RCC. Histopathological assessment of coronal head sections from 80 of the 115 foetuses examined macroscopically was conducted to verify RCC's reporting of "small eyes". The experimental design of the histopathological assessment reflected the primary purpose of the study – to clarify the findings of "small eye". The number of foetuses examined was not comparable across groups, skewing the incidence data, and the assessment was not blinded, nor evaluated by litter. Whilst the conclusions of Cartwright & Wright (2008) support the foetal observations, it is important to note that they do not supersede them. Syngenta changed CRO during isopyrazam development, which necessitated changing rabbit strain – due to limited breeders and users of the Himalayan rabbit. Preliminary and definitive prenatal developmental toxicity studies were conducted at WIL Research Laboratories (Ashland, US) in New Zealand White rabbits. In the preliminary study in New Zealand Whites, a higher incidence of microphthalmia was noted at 1000 mg/kg/day, which was considered related to administration of Isopyrazam. However, the maternal toxicity at this dose level was excessive (severe weight loss and abortion necessitating termination), and a top dose of 500 mg/kg/day was selected for the definitive developmental toxicity study. Increased liver weight and centrilobular hepatocyte hypertrophy was noted in New Zealand White rabbits from 150 mg/kg/day. In the definitive regulatory rabbit study, there were no occurrences of malformations outside of the laboratories historical control data range. The applicant believes that microphthalmia / small eyes in one species at dose levels exhibiting excessive toxicity and marked perturbations in liver function, can only constitute some evidence. The evidence is not sufficiently clear for Category 1b 'Presumed human reproductive toxicant' (H360D). The lack of any evidence of a treatment related increase in major malformations in the definitive regulatory studies should be considered the most significant factor in the judgement that there is insufficient evidence to support classification in Category 1b. Category 2 'suspected of damaging the unborn child' (H361d) is considered the only suitable remaining category. Technical Position on the Classification of Isopyrazam for Developmental Toxicity in Rabbits attached to support above statement. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20191121 CLH submission isopyrazam _Non-confidential.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20191121 CLH submission isopyrazam _Confidential.zip				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2019	France		MemberState	12
Comment received				
FR: Acute oral toxicity: No data are available on isopyrazam containing 15% of the anti isomer. Acute oral toxicity studies showed LD50 > 2000 mg/kg bw with a batch containing 93:7 syn:anti isomers and LD50<2000 mg/kg bw with a batch containing 70:30 syn:anti isomers. Therefore, it cannot be excluded that the LD50 would be less than 2000 mg/kg bw with isopyrazam containing 15% of the anti isomer and a classification Acute Tox 4 is proposed.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium		MemberState	13
Comment received				
Concerning the oral route, BE CA is of the opinion that the up-and-down procedure (OECD 425; anonymous 2008a) performed on rats with isopyrazam (syn:anti ratio 70:30) should be considered with more attention and not be taken as additional information. We note that this CLH proposal is intended for isopyrazam containing a maximum of 15% of the anti enantiomer; but as the provisional ISO name correlated with this substance can contain up to 30% of the anti enantiomer, a classification as acute tox. 4; H302 should be considered.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium		MemberState	14
Comment received				
BE CA acknowledges that the liver is the target organ of Isopyrazam, as this organ is consistently affected across the studies (mostly statistically significant increased relative liver weight, hepatocellular hypertrophy, increased hepatic enzymes and cholesterol…), and in different species (rat, mouse, rabbit, dog…). However, or most of adverse the effects appear at doses not relevant for classification or the effects seen at doses relevant for classification are not considered as severe enough to trigger a classification as STOT RE.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2019	Germany		MemberState	15
Comment received				
We agree with the proposal of classification for environmental hazards as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410 and the acute/chronic M-factor of 10. Supplemental information is available for the degradation product "metabolite CSCD465008". There is another valid test for freshwater algal growth inhibition according to OECD Guideline 201 with Pseudokirchneriella subcapitata SAG.61.81 (Zmijowski, G., 2009). Relevant endpoints are EyC50 (72 hours) = 22.44 mg/L, ErC50 (72 hours) = 26.52 mg/L and NOEC (72 hours) -= 18 mg/L. These data are not relevant for classification and labelling of isopyrazam itself, but relevant for submitted Annex IV - Ecotoxicity degradant				

information in the active substance approval process.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2019	Sweden		MemberState	16
Comment received				
p. 93-114; Evaluation of environmental hazard: The Swedish CA agrees with the proposed environmental classification; Aquatic Acute 1, H400 (Acute M-factor = 10) and Aquatic Chronic 1, H410 (Chronic M-factor = 10). This classification proposal is based on several studies evaluated earlier during the process under Directive 91/414/EEC considering evaluation of active substances of plant protection products. Technical isopyrazam contains a mixture of two diasteroisomers designated syn and anti-isomers. Both of the isomers are considered to be biologically active. However, toxicity testing with fish indicates that the anti-isomer may be more ecotoxic than the syn-isomer. The Swedish CA therefore agrees to exclude the study on the anti-isomer and only include studies with a representative mixture of the two isomers as has been done in the proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2019	France		MemberState	17
Comment received				
FR agrees with the proposed classification and M factors.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium		MemberState	18
Comment received				
BE CA supports the proposed environmental classification based on the data in the CLH dossier: Aquatic Acute 1, H400 ; M=10 Aquatic Chronic 1, H410 ; M=10 A clear difference in toxicity in fish was observed between the syn and anti-isomer, with higher toxicity observed for the anti-isomer. This is also reflected in the outcomes of the 90:10 versus 70:30 syn:anti isomer ratios where the latter showed higher toxicity (1 order of magnitude). The same trend is also observed in the Daphnia magna studies performed with both ratios. Unfortunately, studies with algae were only performed with 90:10 syn:anti ratio and results might does not reflect the true toxicity. Some editorial or/and minor comments : Table 67: for the study with Lemna gibba a static study regime is mentioned, while a semi-static is mentioned in the description of the study underneath				

PUBLIC ATTACHMENTS
1. 20191121 CLH submission isopyrazam _Non-confidential.zip [Please refer to comment No. 3, 8, 11]

CONFIDENTIAL ATTACHMENTS
1. 20191121 CLH submission isopyrazam _Confidential.zip [Please refer to comment No. 3, 8, 11]