Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

***N*-{2-[[1,1'-bi(cyclopropyl)]-2-yl]phenyl}-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide; sedaxane**

EC Number: -
CAS Number: 874967-67-6

CLH-O-0000001412-86-280/F

Adopted

15 March 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON *N*-{2-[[1,1'-BI(CYCLOPROPYL)]-2-YL]PHENYL}-3-(DIFLUOROMETHYL)-1-METHYL-1*H*-PYRAZOLE-4-CARBOXAMIDE; SEDAXANE

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: *N*-{2-[[1,1'-bi(cyclopropyl)]-2-yl]phenyl}-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide; sedaxane
EC number: -
CAS number: 874967-67-6
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2018	Switzerland	Syngenta	Company-Manufacturer	1
Comment received				
Syngenta generally supports the classification as proposed by the dossier submitter (DS), ANSES, except for the hazard class carcinogenicity for which it is commented separately. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Sedaxane Classification Public consultation submission - public attachments.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Sedaxane Classification Public consultation submission - confidential attachments.zip				
Dossier Submitter's Response				
As regard the potential mode of action underlying tumours formation, it is noteworthy that a high concern regarding the use of SDHIs (succinate dehydrogenase inhibitors) as fungicides in agriculture has been recently raised by researchers and clinicians from French institutes with respect to the carcinogenic potential linked to the SDH inhibition (Benit et al, 2018). ANSES decided to set up an emergency expert group to analyse the alert issued, and to identify whether immediate actions or additional risk management measures for the active substances and related products containing SDHI active substances should be taken. Its conclusions are expected for the end of 2018. ANSES has informed EFSA, ECHA, DG Heath and Food Safety and Competent Authorities by post and email. This issue was also discussed during the PRAS meeting of another SDHI fungicide (Pydiflumetofen) in September 2018. A member of ECHA attended this meeting by teleconference.				

Sedaxane belongs to this family with its fungicidal mode of action based on inhibition of the succinate dehydrogenase, a crucial enzyme being at the crossroad between the Krebs cycle and the respiratory chain (complex II). It should be noted that this alert does not concern only sedaxane but is related to all the active substances sharing this same fungicide mode of action via the inhibition of succinate dehydrogenase (SDHI chemical class fungicide). Briefly, 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 tumor 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).
RAC's response
The comments are noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
27.07.2018	Italy	Federchimica	Industry or trade association	2
Comment received				
Federchimica agrees with the DS conclusion in the CLH report that the observed liver tumours and the thyroid adenomas do not trigger classification based on the clear data presented. However, we do not agree with the assessment by DS on the uterine tumours because the overall weight of evidence demonstrates that the observed uterine tumours are not relevant to human due to fundamental differences in physiological control of reproductive senescence between humans and rats. Therefore, there is no risk for humans to develop uterine tumours after long term exposure to sedaxane. No carcinogenicity classification is warranted for sedaxane based on the extensive database presented in support of the mode of action for the observed uterine tumours. The available data for sedaxane and supporting data from structurally related molecule isopyrazam provide convincing evidence for the proposed mode of action for the observed shift in tumor profile in rats treated with sedaxane at 3600 ppm in the rat carcinogenicity study. The key events for the proposed MOA are well-described in the scientific literature, and the shift in tumor incidence is dependent on a marked and sustained deficit in body weight gain occurring in the female Han Wistar rat. The different tumor outcomes observed at 1200 ppm and 3600 ppm sedaxane indicate that the observed dose-response for the decrement in body weight gain translates into a dose response and threshold for the consequential shift in tumor incidence. In addition, the physiological control of reproductive senescence in humans are fundamentally different from those that occur in the rat, the proposed MOA is not relevant for human risk. Therefore, the uterine tumors that develop associated with sedaxane treatment should not be considered in evaluating the risk for adverse health outcomes (e.g., carcinogenicity) after long term exposure to sedaxane.				
Dossier Submitter's Response				
Since the mode of action in rats is not considered sufficiently substanciated by specific experimental data, the assessment of its potential human relevance is unwarranted.				

RAC's response
The comments are noted. Rapporteurs agree with the DS. The mechanistic data do not provide sufficient evidence to support the postulated MoA regarding the uterine tumours.

Date	Country	Organisation	Type of Organisation	Comment number
23.07.2018	Netherlands		MemberState	3

Comment received

For the substance sedaxane, tumors were observed in a 2-year chronic toxicity/carcinogenicity study (OECD 453) in rats and a 2-year carcinogenicity study (OECD 451) in mice. In rats, oral administration with sedaxane resulted in a statistically significantly increased incidence (though not outside of HCD range) of uterine adenocarcinomas in females at a dose of 3600 ppm, and increased incidences (not statistically significant) of hepatocellular adenoma (outside HCD range), thyroid follicular adenoma (outside HCD range), and thyroid follicular cell carcinoma at 3600 ppm in males. In mice, a significant increase in hepatocellular adenomas (outside HCD range) and hepatocellular adenomas and carcinomas combined was observed at 7000 ppm in males.

For this substance, there is an ongoing debate about the relevance of the observed rodent-tumors to human health. In 2011, US-EPA classified sedaxane as "Likely to be Carcinogenic to Humans". The following year EFSA regarded sedaxane not carcinogenic, and after reconsideration, EFSA suggested a Carc. 2 classification for the chemical in 2013. Following these evaluations, the applicant performed mechanistic studies to propose a mode of action (MoA) for the uterine-, thyroid- and liver tumors observed in rodents, and concluded that these tumor types are not relevant to humans.

- Liver and thyroid tumors

The NL MSCA considers the MoA for liver tumours (via the CAR/PXR pathway) and thyroid tumors (CAR-mediated hepatic UGT activation) sufficiently supported by the mechanistic data. Other MoAs are adequately excluded, and the CAR/PXR pathway and CAR-mediated UGT induction seems the only relevant pathway by which these tumors may develop. Consequently, these tumor types are not considered relevant to human health.

- Uterine tumors

The NL MSCA does not consider the MoA for uterine adenocarcinoma in rats, proposed by the applicant, sufficiently plausible. The applicant proposed decreased body weight gain as the 'molecular initiating event'. However, as the DS remarks, decreased body weight gain does generally not lead to tumor development (this effect is commonly seen at high-dose groups). Furthermore, not all key events of the proposed MoA for the development of uterine tumors in female rats are sufficiently supported by the provided mechanistic data. Hence, the proposed MoA does not illustrate why sedaxane in specific would cause uterine adenocarcinomas.

Uterine tumors are seen upon exposure to the structurally related SDHI fungicide isopyrazam in rats. This may suggest a similar MoA for these two chemicals, dependent on chemical structure. Is more information available on structurally related SDHI fungicides and their MoA for uterine tumours?

In conclusion, human relevance of the uterine tumors observed cannot be excluded based

on the uncertainty involved in the MoA of sedaxane for uterine tumorigenesis. Therefore, the NL MSCA shares the opinion of the DS that classification of sedaxane as Carc. 2 is warranted based on the uterine tumors observed in female rats.
Dossier Submitter's Response
Thank you for your support.
RAC's response
The comments are noted.

Date	Country	Organisation	Type of Organisation	Comment number
23.07.2018	Germany		MemberState	4
Comment received				
Based on the CLP Report (provided by the DS), the classification of the substance as a carcinogen cat 2 is supported based on significant increase in incidences of uterine adenocarcinomas in female rats, liver adenomas in male rats, liver adenomas in male mice and liver carcinomas in male mice. Assessment of postulated MoAs resulted in the overall conclusion that human relevance of all the observed tumours may not be discounted and classification is considered to be applicable. Evaluation of the strength of evidence as well as consideration of the additional relevant information suggests that classification as a carcinogen would be applicable and following considerations should be critically discussed: 1. The definition of "sufficient" evidence was partially met (CLP Annex I, 3.6.2.2.3), due to the 2-fold increase in liver carcinomas in mice over the concurrent control and HCD supported with the occurrence of liver adenomas in two species, mice and rats accordingly. 2. Observed tumour may also occur in humans (uterus, liver, thyroid). 3. Incidences of observed tumours are outside the HCD: follicular adenoma in male rats (15% vs 6% Ctrl and 2-11% HCD range), liver adenoma in male rats (10% vs 2% Ctrl and 0-3% HCD range) , liver adenoma in male mice (30% vs 14% Ctrl and 10-28% HCD range), liver carcinoma in male mice (20% vs 10% Ctrl and 6-10% HCD range). 4. The tumours are not of spontaneous tumour types (liver tumours ware observed in Crl:CD-1(ICR), but not in B6C3F1 mice). 5. Multiple site response in male rats was observed. 6. Uterine tumours in female rats and liver tumours in male mice progressed to malignancy. 7. Regarding the postulated MoA for uterine tumours, in support of the position of DS, submitted experimental data were inconclusive to substantiate the postulated MoA. The proposed mechanism is plausible, but it is not supported by findings in studies with other substances that lead to profound weight loss in female rats (e.g. diflufenican, dithianon, diuron). Besides, in the studies that have investigated effects of reduced food consumption on reproductive senescence in rats (e.g. Merry, Holehan 1979), findings of uterine tumours were not reported. Appropriateness of chosen statistical analysis method of experimental data for tyrosine				

hydroxylase expression on mRNA and protein level in TIDA neurons is questioned (this is one of the key experiments provided to support the reasoning the TIDA neurons are functionally superior in 3600 ppm treated rats in comparison to control female rats). Supporting the conclusion of the Dossier submitter, higher protein levels of tyrosine hydroxylase were observed in 1200 ppm treated females (p,143), but not in 3600 ppm. In 1200 ppm treated females, 20% of females were effected with mammary gland fibroadenoma, in the contrary to the proposed by the applicant suppression of mammary proliferation caused by the supressed prolactin.

8. For liver tumours in mice and rats CAR/PXR mechanism is postulated, however:
There is insufficient information in the appendix provided by the dossier submitter on the conditions of the key experiment in which the proliferation of human hepatocytes and DNA replication was investigated in comparison to rodent hepatocytes. The data on the human cell response to the positive and negative control as well as data showing the response of cells to the Sedaxane treatment are essential for the acceptance of dismissal of the postulated MoA. The key species difference in response to the CAR activators is lack of the DNA synthesis in human hepatocytes. Thus, it is crucial to provide for regulatory assessment the results of the following study: Vardy, A. (2016b). Sedaxane – Enzyme and DNA-Synthesis Induction in Cultured Male Human Hepatocytes.Task number TK0172610, Report number CXR1567, Regulatory document number Unknown. Unpublished study conducted by CXR Biosciences Ltd., Dundee, UK. Currently the study is only briefly summarised in the CLP report, p. 224.

Editorial comments:
On page 30 of the CLH-Report it is stated: „Statistically significant increased incidence of uterine adenoma in females at 3600 ppm and reduction in mammary gland and anterior pituitary tumours." In the following table it seems that the increase refers to adenocarcinoma and not adenoma. This should be harmonized.

On page 46 and 47 in table 35 the historical control data are given in the column „Tumour type and background incidence". For both „Thyroid follicular cell adenoma" and „Thyroid follicular cell adenomas/carcinomas combined" a range of 0-3% is mentioned while in table 32 on page 31 a range of 2-11% is cited for „Thyroid follicular cell adenoma" and a range of 0-6% is given for „Thyroid follicular cell carcinoma". No range is mentioned there for „Thyroid follicular cell adenomas/carcinomas combined". These differences between table 32 and 35 should be adjusted.

With regard to the background incidence of uterine adenocarcinoma it is stated on page 48 that ten studies could be considered as historical controls while on page 31 the footnote a of the respective table mentions only 5 HCD. This should be clarified.

Dossier Submitter's Response

Thank you for your support.

The study Vardy, A. (2016b). Sedaxane – Enzyme and DNA-Synthesis Induction in Cultured Male Human Hepatocytes is reported (summary OECD format) in Sedaxane –EU-CLH Report Annex 1 submitted to ECHA along with the CLH report.

Editorial comment:

- On page 30, there is a typo in the text; the increase refers to adenocarcinoma and not adenoma.
- The background incidences are : 2-11% (mean: 6.8%) for follicular cell adenoma, 0-6% (mean: 1.8%) for follicular cell carcinoma and 2-15% (mean: 8%) for follicular cell adenoma/carcinoma combined (Typo in in table 35). Please refer also to Sedaxane –EU- CLH Report Annex 1 point 3.9 page 115.
- The background incidence of uterine is based on 10 studies (typo in the footnote page 31). Please refer also to Sedaxane –EU- CLH Report Annex 1 point 3.9 pages 113-114.

RAC's response

The comments are noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2018	Spain		MemberState	5

Comment received

In 2011, US-EPA classified sedaxane as "Likely to be Carcinogenic to Humans." This classification was based on the presence of tumours at multiple sites in two species: liver and thyroid tumours in male rats, uterine tumours in female rats, and liver tumours in male mice.
It was also concluded that the overall pattern of tumours in rats and mice suggests that a 'Carc cat 2, H351 classification regarding carcinogenicity would be required for sedaxane (EFSA, 2013). Since that time, the applicant has generated mechanistic studies and has proposed modes of action for liver, thyroid, and uterine tumours.

Liver tumours:

Based on the available data, The Spanish CA agrees with the Dossier Submitter opinion that there is enough evidence to support the postulated MoA (CAR activation) to be the underlying MoA of liver tumours observed in rodent males. Similarly to phenobarbital (known CAR inducer), sedaxane did not induce DNA replication (prerequisite for tumour formation) in human hepatocytes following induction of human CAR, in contrast to rat. Due to this qualitative difference, the liver tumours as a result of CAR activation by sedaxane are considered to be of little relevance to humans. The available data also permitted to adequately rule out alternative MoAs (i.e., genotoxicity, peroxisome proliferation, AhR induction, cytotoxicity, estrogenic stimulation, statins, infections, iron/copper overload, and increased apoptosis).

Therefore, liver tumours observed in male rats and male mice at high dose levels do no trigger classification for carcinogenicity as the MoA is considered not relevant to humans.

Thyroid tumours:

Based on the available data, The Spanish CA agrees with the Dossier Submitter that there is enough evidence to support the postulated MoA (CAR-mediated induction of hepatic UGT activity) to be the underlying MoA of the slight increased incidence of thyroid adenomas observed in high dose male rats. The increase in the activity of hepatic UDPG-transferase results in increased clearance of thyroid hormone levels (T4), resulting in thyroid stimulation. Such a mechanism cannot be directly extrapolated to humans due to T4 binding protein that greatly reduces susceptibility to plasma T4 depletion. ECHA CLP Guidance (2017) lists "certain thyroid tumours in rodents mediated by UDP

glucuronyltransferase (UGT) induction (IARC, 1999; EU Specialised Experts, 1999)" as not relevant to humans. Besides, the available data permitted to rule out alternative MoAs: genotoxicity and inhibition of thyroid peroxidase (TPO) peroxisome proliferation. Indeed sedaxane was negative according to genotoxicity package and was not an inhibitor of rat thyroid peroxidase activity in vitro.

Therefore, thyroid tumours observed in male rats at high dose levels do no trigger classification for carcinogenicity as the MoA is considered not relevant to humans.

Uterine tumours:

The applicant argues that the proposed MOA for the increased incidence in uterine adenocarcinomas observed in female Wistar rats at 3600 ppm after administration of sedaxane for 2 years (Anonymous, 2010), has been well characterized and described in Wistar rats (Harleman et al., 2012), and rats tested in lifetime dietary restriction studies (Roe et al., 1995; Tucker, 1979), where the same pattern of changes as with 3600 ppm sedaxane treatment was observed (i.e., lower body weight gain plus lower incidences of pituitary adenomas and mammary gland fibroadenomas, and higher incidences of uterine adenocarcinomas).

In the MoA proposed for the increased incidence in uterine adenocarcinomas observed in female Wistar rats at 3600 ppm, the applicant postulates that the higher incidence of uterine tumours in female rats is attributable to a large deficit in body weight, which results in changes/delay in reproductive senescence by preserving the dopaminergic neurons of the hypothalamus. The continued high dopamine activity has a tonic inhibitory effect on prolactin release by the pituitary. Specifically for Wistar rats, this change (mediated via a state similar to caloric restriction) compared to normal aging control rats leads to a lower incidence of tumours in the pituitary and mammary glands, and a higher incidence of uterine adenocarcinomas. This same pattern of changes in Wistar rats has been demonstrated to occur in rats maintained for their lifetimes on a restricted calorie diet. The suppression of the age-related increases in prolactin levels by sustained dopamine activity results in changes/delay in reproductive senescence and consequently greater cumulative exposure of the uterus to a higher estrogen:progesterone ratio (i.e., reduced progesterone dominance of estrogen) in aged female rats, which would lead to a proproliferative estrogenic stimulation of the uterine endometrial cells. Over time, the estrogenic proliferative drive leads to promotion of spontaneously initiated uterine adenocarcinomas. At the same time, the decreased prolactin signalling leads to decreased proliferation of the anterior pituitary and mammary glands, which in turn leads to lower incidences of pituitary adenomas and prolactin driven mammary gland fibroadenomas. The control of the female reproductive cycles and the drivers for reproductive senescence in humans are fundamentally different than that in rats, and therefore, it is postulated that this MOA for uterine tumours in rats is not relevant to human risk assessment due to qualitative differences between the species.

The dossier submitter claims that the experimental data do not provide enough evidence to support the postulated mode of action of rat uterine tumours induced by sedaxane (several deficiencies were identified and some key events were not substantiated by experimental data).
French CA in the absence of an established MoA considered that classification for carcinogenicity is warranted.

However in our opinion, it is more important the comparison with the historical control

data. The fact is that, the slightly statistically significant increased incidence in uterine adenocarcinomas in Wistar rat at 3600 ppm compared to concurrent controls was within the range of historical control data from the test laboratory during the period (2002-2012).

In our view, uterine adenocarcinoma is a common finding in aging Wistar rats, as demonstrated by historical control data from the same laboratory. In conclusion, the Spanish CA considers that the increased incidence of uterine carcinoma observed female rats is considered as weak and inconsistent evidence and not sufficient to warrant carcinogenicity classification.

Dossier Submitter's Response

It is acknowledged that uterine adenocarcinoma is a common finding in aging Wistar rats and uterine adenocarcinoma incidence in the concurrent control animals was Low (0%). However, as shown in the Historic control data from the same laboratory two other studies out of the ten during this period (2002-2012) had a control group with a 0.0% incidence. As regard HCD from RITA database, they are not considered appropriate (not the same laboratory). Furthermore, regarding structure-activity relationships, another SDHI fungicide similar to sedaxane, "isopyrazam" also induced uterine adenocarcinoma at a high dose level of 3000 ppm (233 mg/kg/day). Therefore, the statistically increased incidence of uterine tumours observed at high dose level (3600 ppm), above the HCD mean could not be ruled out as unrelated to treatment.

RAC's response

The comments are noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2018	Belgium		MemberState	6

Comment received

Two GLP studies are available to evaluate the carcinogenic potential of sedaxane. The OECD TG 453 oral rat study (0-200-1200 and 3600 ppm, 52/sex/group) showed 17% of uterine adenocarcinoma ($p<0,01$) and thyroid follicular cell adenoma/carcinoma, associated with thyroid and liver hyperplasia at top dose (261 mg/kg in females or 218 mg/kg in males). First effects on liver and thyroid started from 1200 ppm (12% combined thyroid follicular cell adenoma/carcinoma). A mouse OECD TG 451 study (0-200-1250-7000 ppm, 50/sex/group) also showed a statistically significant increase in hepatocellular adenomas (30%) or combined adenomas/carcinomas (40%). Several investigative or mechanistic studies were also proposed to explain the potential mode of action for these three sites (uterus, thyroid and liver).
DS concluded that the MoA behind observed liver and thyroid neoplasms after sedaxane exposure was CAR/PXR mediated, therefore considered not to be relevant to human. A MoA has also been proposed to explain the uterine adenocarcinomas observed in rat. The DS concluded that the experimental data did not provide enough evidence to support this postulated mode of action and therefore proposed a Carc 2 classification based on the observations of uterine neoplasms in rat. We concur with this conclusion. Please find further considerations :
- The decrease in adipose tissue is not sufficiently demonstrated, due to the absence of related specific data's. Moreover, the non-statistically significant decrease in leptin might be view as an adaptative reaction to the non-specific decreased body weight gain induced by sedaxane. In any case, we would expect to some extent an increased appetite

associated with lower levels of leptin, an anorectic hormone. However, in the two carcinogenicity studies, we observe a decrease in food consumption and/or food utilisation. Therefore, some uncertainties remain regarding the relation between the investigative study on leptin levels, driven on frozen 1-year serum samples, and the results showed in the carcinogenicity studies. - A potential association between leptin levels and TIDA neurons after sedaxane exposure is only speculative. No data is available to demonstrate this relation. - The increase in prolactin levels after sedaxane exposure are not sufficiently demonstrated and their causality on uterine tumours are only speculative.
Dossier Submitter's Response
Thank you for your support.
RAC's response
The comments are noted.

Date	Country	Organisation	Type of Organisation	Comment number
02.08.2018	Finland		MemberState	7
Comment received				
The Rapporteur (ANSES, France) proposed to classify sedaxane as "suspected of causing cancer" Carc 2; H351 based on the increased incidence of uterine carcinomas in rat females. The statistical significant uterine tumor incidence in the rat 2- year study is limited to females in the highest dose (261 mg/kg) group. Although no tumors were observed in concurrent controls, the incidence (17%) is within the range of historical control data (0-19%) and RITA Wistar rat data (0-28%), which can be used as evidence of high rate of spontaneous tumors. Moreover, a significant body weight decrease (50%) in animals at the top dose interferes with the interpretation of the study. FI CA considers that the available data does not provide enough evidence to support classification Car 2.				
Dossier Submitter's Response				
It is acknowledged that uterine adenocarcinoma is a common finding in aging Wistar rats and uterine adenocarcinoma incidence in the concurrent control animals was Low (0%). However, as shown in the Historic control data from the same laboratory two other studies out of the ten during this period (2002-2012) had a control group with a 0.0% incidence. As regard HCD from RITA database, they are not considered appropriate (not the same laboratory). Furthermore, regarding structure-activity relationships, another SDHI fungicide similar to sedaxane, "isopyrazam" also induced uterine adenocarcinoma at a high dose level of 3000 ppm (233 mg/kg/day). Therefore, the statistically increased incidence of uterine tumours observed at high dose level (3600 ppm), above the HCD mean could not be ruled out as unrelated to treatment.				
RAC's response				
The comments are noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2018	Switzerland	Syngenta	Company-Manufacturer	8

Comment received

Syngenta does not agree with the assessment by DS, ANSES, that the uterine tumours trigger classification for sedaxane based on the human non-relevance of the observed effects in rat. This non-relevance is based on the fundamental physiological differences between humans and rats with regard to reproductive senescence as well as the role of prolactin during reproductive cycles. The hormonal control of the hypothalamic-pituitary-gonad (HPG) axis and the changes that occur in the transition from normal reproductive function into reproductive senescence are fundamentally different between rats and humans. In the rat, the failure of hypothalamic control drives reproductive senescence while in the human, the depletion of the limited number of available follicles within the ovaries results in reproductive senescence. Menopause in humans is associated with a marked decrease in circulating estrogens and progesterone.

The human reproductive cycle (menstrual cycle) has very different control mechanisms compared to rats, which have 4-5 day estrous cycles. First, the surge of prolactin during proestrus in rats is not observed in human menstrual cycles. Second, the luteotrophic actions of prolactin in the rat is not present in humans.

In addition, there are fundamental differences between humans and rats in the physiological controls that drive reproductive senescence. Menopause and reproductive senescence in humans are driven by an eventual depletion of a limited number of primordial follicles in the ovaries with age. Reproductive senescence in the rat is driven by the brain, namely the failure of hypothalamic control. Moreover, it is well known that menopause in human females is associated with a marked decrease in circulating estrogens and progesterone. Persistent estrus is unique to rats, and there is no equivalent state in humans. Therefore, uterine tumours observed in the 2-year sedaxane carcinogenicity study at the high dose as a consequence of an increased duration of a persistent estrus state would not be observed in humans.

The key events of the mode of action (MOA) for uterine tumours in female Han Wistar rats are well-described in the scientific literature as referenced in documents attached. The available data for sedaxane presented in the CLH report support these key events well. To complete the overall assessment and address the data gaps noted by the dossier submitter, Syngenta has recently completed additional investigations into the proposed MOA for the observed shift in tumor profile in rats treated with a structurally related SDHI, isopyrazam. Isopyrazam shows a similar uterine tumour profile in the 2-year carcinogenicity as sedaxane (i.e. increased uterine tumours with a concomitant decrease in mammary gland fibroadenomas and pituitary adenomas); therefore, the new isopyrazam data provide convincing evidence supporting the MOA for sedaxane. The additional data are submitted along with this overview and consist of the following:

1) An 18-Month Investigative Dietary Study in the Female Han Wistar Rat: File name: Isopyrazam - 18-Month Investigative Dietary - Female Han Wistar Rat; Doc ID SYN520453_11946 (confidential), SYN524464_11751 (redacted);

2) The OECD summary of the 18-Month Investigative Dietary Study in the Female Han Wistar Rat: File name: Isopyrazam - OECD summary - 18 month uterine tumour mode of action study; Doc ID SYN520453_11948 (confidential), SYN524464_11752 (redacted);

3) A detailed weight of evidence document describing the MoA and human non-relevance: File name: Sedaxane Statement MOA Human Relevance Uterine Tumours; Doc ID: SYN524464_11754;

4) A short summary addressing the data gaps identified in the MOA by the dossier submitter ANSES in the CLH report: File name: Sedaxane Response to DS Assessment MOA Uterine Tumour; Doc ID: SYN524464_11753

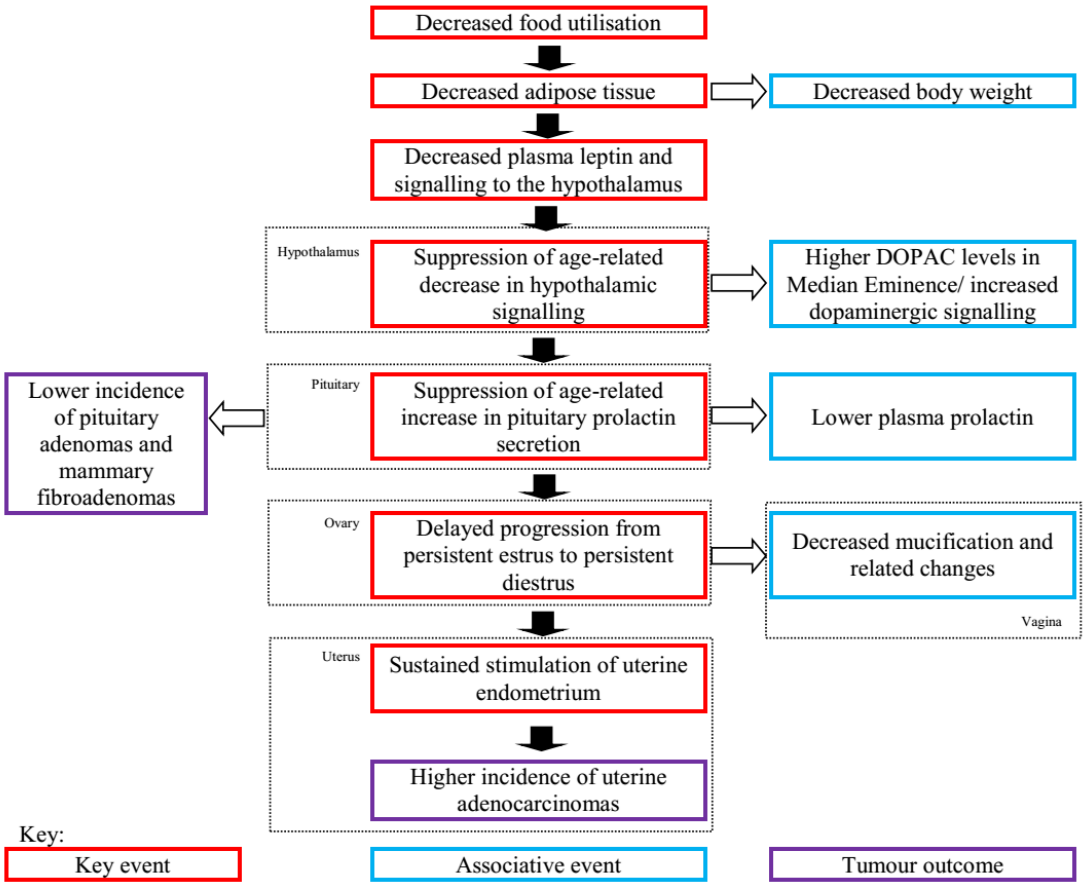
The new data confirm the proposed MOA in rats and the overall database demonstrates that the observed shift in tumour profile, including the higher incidence of uterine tumours, has no relevance to human health.

In light of this new information, sedaxane should not be classified for carcinogenicity.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Sedaxane Classification Public consultation submission - public attachments.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Sedaxane Classification Public consultation submission - confidential attachments.zip

Dossier Submitter's Response

As mentioned above, Syngenta has slightly changed the proposed mode of action (e.g.: initial key event: decreased food utilisation versus decreased bodyweight) event and has submitted another mechanistic study with a structural analogue Isopyrazam to further support it.



DS assessment:
The proposed initial key event is still a broad event. Syngenta argued that contrary to other compounds inducing decreased body weight gain but no increased incidence of uterine tumours, both sedaxane and isopyrazam studies induced atypical pattern of response with decreased food utilisation and body weight deficit sustained throughout the entire lifetime of the study.
DS considers that this not typical pattern of response observed with both compounds could be linked to their common fungicidal mode of action (SDH inhibitors) and inhibition of succinate dehydrogenase could be the molecular initiating event. However this is not supported by any specific data.

As regard, the new submitted mechanistic study with isopyrazam, this study substantiated some key events not observed in the data package with sedaxane (e.g.: decreased adipose tissue and statistical decreased plasma leptin and prolactin).
However, as regard suppression of age-related decrease in hypothalamic signalling (higher functionality of TIDA neurons), as already mentioned the evidence was weak with sedaxane (higher protein levels of tyrosine hydroxylase in 1200 ppm treated females than in 3600 ppm, see also German comment). From the data with top dose of isopyrazam, the mean dopamine concentrations in the median eminence of the hypothalamus were only statistically significantly higher at Week 26 and were not affected later. The measure of dopamine turnover in the median eminence was unaffected by treatment. Furthermore, across the time points in this study, the concentration of dopamine (DA) and DOPAC in the median eminence remained fairly constant in the control animals from Weeks 26 through 80. 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. These results do not support a decreased of dopamine with time (up to 80 weeks) and a preservation of the dopaminergic activity with isopyrazam treatment as postulated. While there was no direct sedaxane data on differences in estrous cycling between 1-year and 2 years, the 18-month isopyrazam MOA study suggests that high dose of isopyrazam can delay the time of onset of reproductive senescence. 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. No histopathological findings indicative of overt estrogenic stimulation were observed in sedaxane data package and there were also no definitive adverse test substance-related histologic changes across all time points, and there were no apparent test substance-related effects on proliferative lesions in the uterus, cervix, and vagina in the 18-month isopyrazam MOA study. In conclusion, based on the data submitted with the structural analogue, DS is still of the opinion that the experimental data do not provide enough evidence to support the postulated mode of action of rat uterine tumours induced by sedaxane. Furthermore an alternative potential mode of action through SDH inhibition and accumulation of succinate (considered as oncometabolite) cannot be ruled out in respect to the alert recently raised by researchers and clinicians from French institutes (Please refer to first comment Benit, 2018).
RAC's response
The comments are noted. Rapporteurs agree with the DS. The mechanistic data do not provide sufficient evidence to support the postulated MoA regarding the uterine tumours.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
23.07.2018	Germany		MemberState	9
Comment received				
We support the proposal of classification for environmental hazards as Aquatic acute 1 (H400), Aquatic chronic 2 (H411) and the acute M-factor of 1.				
Dossier Submitter's Response				
Thank you for the positive feedback.				
RAC's response				
The comments are noted, however ther rapporteurs propose Aquatic Chronic 1; H410 with a M-factor of 1.				

Date	Country	Organisation	Type of Organisation	Comment number
11.06.2018	United Kingdom		MemberState	10
Comment received				
The key chronic endpoint is for fish: Pimephales promelas NOEC 0.165 mg/l (mm). This test species was not the most acutely sensitive as the lowest 96-h LC50 of 0.62 mg/l (mm) was for Cyprinous carpio while the P. promelas 96-h LC50 was 0.98 mg/l (mm). Considering the surogate approach using the lowest acute endpoint would result in Aquatic Chronic 1 (M-factor 1) for a non rapidly degradable substance.				

Although both fish species exhibited acute endpoints in the 0.1-1.0 mg/l range, we note the current chronic NOEC is close to 0.1 mg/l. On this basis, we wonder if Aquatic Chronic 1 (M-factor 1) should be considered? It might be useful to consider acute:chronic ratios and if EC10 endpoints are available.
Dossier Submitter's Response
The LC_{50} for *P. promelas* and *C. carpio* belong to the same range of toxicity (less than a factor of 2 between the 2 LC_{50} values). It is assumed that this slight difference is not significant and does not demonstrate a difference in sensitivity between both species. Therefore, sensitivity of the 2 species to sedaxane are considered similar. In addition, the NOEC (165 µg a.i./L) derived for *P. promelas* is considered robust as it corresponds to the highest tested concentration without significant effects while significant effects are obsereved at the highest tested concentration in the study (469 µg a.i./L) No EC_{10} has been provided by submitter and no reliable one can be derived considering the results from the study.
RAC's response
The comments are notes, the rapporteurs agree with the comment from UK MSCA and propose Aquatic Chronic 1; H410 with a M-factor of 1.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2018	Belgium		MemberState	11
Comment received				
BE CA supports the proposed environmental classification by FR CA. The substance warrants classification with Aquatic Acute 1, H400 (M=1) and Aquatic Chronic 2, H411. Sedaxane is not rapidly degradable , does not meet the bioaccumulation criterion and the LC50 and NOEC for the most sensitive species (fish) are resp., 96hEC50= 0.62 mg/L (Cyprinus carpio), 21dNOEC= 0.165 mg/l.(Pimephales promelas).				
Dossier Submitter's Response				
Thank you for the positive feedback.				
RAC's response				
The comments are notes, the rapporteurs agree with the comment from UK MSCA and propose Aquatic Chronic 1; H410 with a M-factor of 1.				

Date	Country	Organisation	Type of Organisation	Comment number
02.08.2018	Finland		MemberState	12
Comment received				
FI CA supports the conclusion that sedaxane is neither rapidly degradable nor potentially bioaccumulative. The lowest acute toxicity was 96 h LC50 value of 0.62 mg/L for fish Cyprinus carpio. The lowest chronic toxici-ty was NOEC value of 0.165 mg/L for fish Pimephales promelas. Based on classification criteria FI CA supports the proposed environmental classification Aquatic Acute 1, H400 with M-factor of 1 and Aquatic Chronic 2, H411 for sedaxane.				
Dossier Submitter's Response				
Thank you for the positive feedback.				

RAC's response
The comments are notes, the rapporteurs agree with the comment from UK MSCA and propose Aquatic Chronic 1; H410 with a M-factor of 1.

PUBLIC ATTACHMENTS

1. Sedaxane Classification Public consultation submission - public attachments.zip [Please refer to comment No. 1, 8]

CONFIDENTIAL ATTACHMENTS

1. Sedaxane Classification Public consultation submission - confidential attachments.zip [Please refer to comment No. 1, 8]