Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

mesotrione (ISO) 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione

EC Number: -
CAS Number: 104206-82-8

CLH-O-0000001412-86-232/F

Adopted

14 September 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON MESOTRIONE(ISO); 2-[4-(METHYLSULFONYL)-2-NITROBENZOYL]-1,3-CYCLOHEXANEDIONE

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: mesotrione(ISO); 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
EC number: -
CAS number: 104206-82-8
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.11.2017	United Kingdom	Syngenta AG	Company-Manufacturer	1
Comment received				
2.2 Short summary of the scientific justification for the CLH proposal (Page 11) 'In the MoA proposed by the applicant, the spectrum of effects seen with mesotrione are said to be due to hypertyrosinaemia, rather than a direct result of dosing with mesotrione. Humans are expected to be less sensitive to the effects of mesotrione than rats, due to a higher innate TAT activity (for further information, see Annex 1). Since the original decision regarding the classification and labelling of mesotrione, other HPPD-inhibitors (namely sulcotrione and tembotrione) have been considered by RAC. Both of these substances have been classified for repeated dose toxicity and reproductive toxicity.' Syngenta comments Mesotrione was first registered in the EU in 2000. An evaluation of the Mode of Action (MOA) of mesotrione was undertaken by Syngenta and it was shown that the mouse is the appropriate model for the assessment of potential adverse effects in man due to similarities in the way that the mouse handles excess tyrosine when compared to humans and significant differences in the way both the mouse and humans handle excess tyrosine when compared to the rat (1) . As a result of the investigations undertaken with mesotrione and the understanding that the mouse was the most appropriate model for human risk assessment, a complete toxicology database was produced in the mouse covering ADME, repeat dose, chronic, carcinogenicity and reproductive toxicity endpoints, confirming that inhibition of HPPD was the only MOA seen with mesotrione and that no other significant toxicity was evident. The endpoints for hazard and risk assessment in the EU in 2000 were based on mouse studies. This approach has been maintained in the recent EFSA review: 'A complete toxicological dossier has been submitted on mice and this species was				

considered a better model in comparison to rats to extrapolate the risk to humans.'(2) Other HPPD inhibitors registered in the EU (sulcotrione and tembotrione) do not have the wealth of data clearly showing the differences in handling excess tyrosine in the mouse and rat. Neither do they have full databases in the mouse that would confirm that no toxicity unrelated to tyrosinaemia is present. Hence endpoints for hazard and risk assessment for these molecules can only be based on rat data.

For mesotrione, the mouse has been shown to be the most appropriate model for the assessment of potential effects in man. EFSA have recently concluded that the mouse is a better model than the rat for the extrapolation of the risk of mesotrione to humans. A full toxicology database is available in the mouse with which to conclude on the appropriate hazard classification for mesotrione. This confirms that no hazard classification is required for mesotrione.

(1) Lewis RW and Botham JW (2013) A review of the mode of toxicity and relevance to humans of the triketone herbicide 2-(4-methylsulfonyl-2-nitrobenzoyl)1-3-cyclohexanedione Crit Rev Toxicol 43(3) 185-199

(2)Peer review of the pesticide risk assessment of the active substance mesotrione EFSA Journal 7th March 2016

During the review of the mesotrione draft CLH dossier, questions were asked as to whether mechanistic studies supporting the proposed mode of action of HPPD inhibitors were available for compounds other than mesotrione. Syngenta have prepared a summary of available data and this is included as a public attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mesotrione proposed classification of STOT_RE FINAL.zip

Dossier Submitter's Response

Thank you for your comments and the supporting documents. The CLH report presents a thorough assessment of the data made available to us at the time of submission.

We note that the available data are supportive of the proposed mode of action (i.e. tyrosinaemia) and that humans are likely to be less sensitive to these effects than the rat. However, we reamin of the opinion that there are uncertainites regarding the overall relevance of certain findings (i.e. the effects in the kidneys and the increase in total litter loss and pre/post natal death) to humans, as there is no information of the relative potency.

Therefore, it is our opinion that the classification proposed in the report is justified.

RAC's response

Thank you for your comment and attachment. RAC agrees with DS's response that humans are likely to be less sensitive to these effects than the rat but that there are still uncertainties regarding relevance of findings to humans. Therefore, RAC considered the classification for the eyes and nervous system justified.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	2
Comment received				
BECA welcomes this proposal to classify mesotrione.				

Dossier Submitter's Response
Thank you for your comments.
RAC's response
Thank you. Noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2017	France		MemberState	3
Comment received				
Page 96: The classification proposal of mesotrione as Repr Cat 2, based on findings observed in the multi- and one-generation studies, is agreed. Moreover, the reduced/delayed ossification observed in the developmental studies in the absence of clear maternal toxicity supports also this classification.				
Dossier Submitter's Response				
Thank you for your support for the classification. It is noted in the report that whilst the incidence of some findings (reduced/delayed ossification) exceeded the laboratory historical controls, the effects were variable and often occurred without a clear relationship to the dose. These effects were therefore not considered to be of sufficient concern for classification.				
RAC's response				
RAC thanks the MSCA for their comment and the DS for their response. As delayed developement was observed in three species in absence of maternal toxicity in mice and rabbits, RAC agrees with MSCA that the growth effects are supportive for the classification. Although variable between species and sometimes without clear dose-response, some of skeletal variations clearly exceeded concurrent controls (mice) or historical controls (rabbit, rat).				

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Spain		MemberState	4
Comment received				
An increase in total litter loss and the incidence of pre/post natal death was observed in the multi-generation and one-generation studies in the rat. Available data are supportive of a correlation between these effects and the level of plasma tyrosine in the dams due to inhibition of HPPD. In the developmental studies in the rat, mouse and rabbit there were also a number of effects indicative of reduced/delayed ossification. Besides, other HPPD-inhibitors (sulcotrione and tembotrione) have been considered by RAC and both of these substances have been classified for reproductive toxicity. We agree with the dossier submitter that, information is lacking regarding the relative potency for reproductive toxicity in humans. Given the uncertainty about the relevance of these effects to humans, the Spanish CA supports the proposal to classify mesotrione with Repr. 2; H361d: Suspected of damaging the unborn child				
Dossier Submitter's Response				
Thank you for your comments, see our response to comment 3 also.				

RAC's response
Thank you for your comments, see our response to comment 3 also.

Date	Country	Organisation	Type of Organisation	Comment number
30.11.2017	United Kingdom	Syngenta AG	Company-Manufacturer	5
Comment received				
Page 96 4.11.5 Comparison with criteria (reproductive toxicity). The authors of the CLH dossier have proposed clasification of mesotrione as a reproductive toxin based on a higher incidence of total litter loss and decreased pup survival in generational studies in the rat. Syngenta believes that a strong weight of evidence supports the position that these findings are attributable to severe tyrosinaemia seen in the rat as a consequence of HPPD inhibition but not seen in the mouse, the most relevant species for human risk assessment. Syngenta have prepared a position paper giving more details of their position, this is available as a public attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mesotrione proposed classification of STOT_RE FINAL.zip				
Dossier Submitter's Response				
Thank you for submitting the position paper. Please see our response to comment 1.				
RAC's response				
Thank you for your comment. Please see our response to comment 1.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	6
Comment received				
Fertility BECA agrees there is a lack of data requiring a classification for fertility effects. Development BECA supports the need for classification for developmental effects considering: - Delay in ossification or retardation of ossification were seen consistently in three guideline studies, on three different species (mice, rat, rabbit) - No clear dose-response relationship could be established but, in a non-negligible number of cases, effects appearing were outside the HCD - Skeletal defects observed (such as a clear impact on cervical bones ossification), warrant a classification - In the mice and rabbit guideline studies, embryotoxic/teratogenic NOAEL was inferior to maternal NOAEL, increasing the concern. Therefore, BECA agrees to classify the mesotrione as reprotoxic for the development and supports the classification as Repr. 2 – H361d.				
Dossier Submitter's Response				
Thank you for your support, see our response to comment 3 also.				
RAC's response				
Thank you for your support, see our response to comment 3 also.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Spain		MemberState	7

Comment received

Following repeated exposure to mesotrione, the eyes and kidneys were identified as the target organs in rats, whereas only the eyes where affected in mice and dogs.

Mesotrione is a triketone herbicide and it exerts its Mode of Action (MoA) via inhibition of the enzyme 4- Hydroxyphenylpyruvate dioxygenase (HPPD). In mammals, HPPD is the second enzyme in the catabolic cascade of tyrosine and the consequence of HPPD inhibition is a dose dependent elevation in plasma tyrosine. In the MoA proposed, the spectrum of effects seen with mesotrione are said to be due to hypertyrosinaemia.

Other HPPD-inhibitors (sulcotrione and tembotrione) have been considered by RAC. Both of these substances have been classified for repeated dose toxicity for the effects observed in the kidney. For tembotrione, RAC also considered the effects observed in the eyes to support the classification for repeated dose toxicity.

Effects in the eye

The effects in the eyes observed with mesotrione are considered to be of significant concern (ocular opacity as a result of corneal keratitis, epithelial disruption and associated vascularization) and were observed at doses below the relevant guidance values for classification (i.e., from 0.71 mg/kg bw/d in male rats in a guideline 90 day study). In the MoA proposed, the effects in the eye are said to be due to hypertyrosinaemia.

Data are available from human studies in which individuals received either mesotrione or NTBC (a triketone which is used therapeutically in humans to treat hereditary hypertyrosinaemia type 1). NTBC has been shown to greatly increase tyrosine concentrations in healthy adult volunteers treated with a single dose of 1 mg/kg bw/day NTBC and to cause eye problems in some children treated with 1 mg/kg bw/day NTBC (against Type 1 hypertyrosinaemia). These studies provide evidence to show that mesotrione is ~400 times less potent than NTBC. Given that NTBC is a more potent inhibitor of HPPD (400 fold greater) than mesotrione, it can be expected that plasma tyrosine levels will not exceed to cause similar effects in humans repeatedly dosed with mesotrione. Therefore, eye effects are not expected to occur in humans at doses below those relevant for classification.

Effects on the cornea were also seen in rats repeatedly dosed with Tembotrione, RAC concluded that the potency of tembotrione in humans was thought not to be that much lower than the potency of NTBC and therefore tembotrione was expected to have an intrinsic possibility to also cause similar effects in humans. Concerning human sensitivity in relation to the animal data, RAC concluded that this might be intermediate to that of the very sensitive rat and the non-sensitive mouse. RAC therefore considered that the findings in the rat studies were relevant to humans and the proposal to classify tembotrione as STOT RE Cat 2 was also based on the effects on the eyes. However, RAC used data on sulcotrione in monkeys, and data from studies on mesotrione, to conclude that the corneal effects resulting from administration of sulcotrione were not relevant to humans due to species-specific differences in tyrosine catabolic pathways the rat, especially the male, is particularly sensitive to these effects.

Overall, the Spanish CA agrees with the dossier submitter that the ocular effects observed with mesotrione do not support classification for STOT-RE.

Effects in the kidney

The kidney was a target organ in rats only, with males being more sensitive than females. A number of effects were seen in the available repeated dose toxicity studies with mesotrione (subchronic and chronic) and in a guideline multigeneration study in rats. It is difficult to dismiss the effects entirely (especially the renal pelvic dilatation and the chronic progressive glomerulonephropathy). The chronic progressive glomerulonephropathy was observed in a 90-day oral rat study at a dose level of 14.5 mg/kg bw/day. Effects were noted at lower dose levels in the 2-year carcinogenicity study (from 0.48 mg/kg bw/day) and the multigeneration study. It is likely that these effects are associated with the tyrosinaemia, but definitive evidence is not available to demonstrate that this is the case. Furthermore, there is no evidence regarding the relevance of the effect in humans, and therefore, they cannot be dismissed.

With regards to the effects seen in the kidneys, RAC considered that classification with STOT RE 2 (kidneys) was appropriate for sulcotrione and tembotrione.

Overall, the Spanish CA considers that the available data support the proposal of the dossier submitter to classify mesotrione with STOT-RE 2; H373 – May cause damage to organs (kidneys) through prolonged or repeated exposure.

Dossier Submitter's Response

Thank you for your comments.

RAC's response

Thank you for your comment.

With regards to kidney effects, in the 90-day studies, although chronic progressive glomerulopathy (CPG) was increased at 14.5 mg/kg bw/day in one guideline study, the second guideline study in rats showed that such effects were not observed at higher dose levels (112, 1 111 mg/kg bw/day). Kidney effects observed in the multigenerational study did not occur in first parental generation and have therefore been considered for developmental toxicity. Finally, the increase in the severity of CPG, mainly in male rats, in the 2-year study has been considered insufficient for classification.

With regards to the eyes, RAC noted that there are uncertainties on human sensitivity to such effects. For treatment with NTBC, the threshold plasma tyrosine level recommended to avoid ocular effects has been lowered to 500 µmol/L by US FDA in 2018. Moreover, although mesotrione has been shown to be less potent than NTBC, only a low number of individual were used in the volunteer study (n=6) and repeated exposure was not investigated. Overall, the ocular findings are considered relevant to humans. As there are uncertainties in the relative potency, eye effects were considered relevant for classification STOT RE 2. Additionally, nervous system was also considered as a target organ of mesotrione.

Date	Country	Organisation	Type of Organisation	Comment number
30.11.2017	United Kingdom	Syngenta AG	Company-Manufacturer	8
Comment received				
Page 67 4.8.1: Summary and discussion of repeated dose toxicity findings relevant for classification as STOT-RE The authors of the CLH dossier have suggested that mesotrione be classified as STOR_RE on the basis of kidney effects noted in repeat dose and reproductive toxicity studies in the rat. Syngenta believes that of the effects noted by the authors, some are incidental to treatment and others are attrbutable to severe tyrosinaemia seen in the rat as a result of HPPD inhibition but absent in the species most relevant to human risk assessment, the mouse. Syngenta has prepared a paper outlining the the reasons for its position and this is included as a public attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mesotrione proposed classification of STOT_RE FINAL.zip				
Dossier Submitter's Response				
Thank you for providing the position paper. Please see our response to comment 1.				
RAC's response				
Thank you for providing the position paper. Please see our response to comment 1.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
29.11.2017	Finland		MemberState	9
Comment received				
Toxicity tests with aquatic macrophytes (Lemna gibba) are valid for classification purposes of aquatic hazards. According to growth rate reduction on frond number and dry weight, the acute toxicity EC50 value of mesotrione is between 10-100 µg/l and the chronic toxicity NOEC value is between 1-10 µg/l. FI CA supports the conclusions that the substance is neither rapidly degradable nor potentionally bioaccumulative. Based on the available information and the classification criteria FI CA supports to modify the current classification of Aquatic Acute 1, H400 with M-factor of 10 and Aquatic Chronic 1, H410 with M-factor of 10 for mesotrione.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted. Thank you for your comment				

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2017	France		MemberState	10
Comment received				
We agree with the classification and M factors (acute and chronic) proposals.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Noted. Thank you for your comment

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Germany		MemberState	11
Comment received				
p. 121 summary of relevant information on aquatic toxicity, Green microalgae Pseudikirchneriella subcapitata: The endpoint listed in the table does not match the endpoint given in the RAR. The RAR lists a 72-hr EbC50: 3.5 mg/L. Navicula pelliculosa: The EC50 endpoints listed in the table do not match the endpoints given in the DAR. Please correct. p. 126, 5.4.3 Algae and aquatic plants, Study 1: According to the RAR the NOErC is 1.5 mg a.s./L. Here as well, the EbC50 is given differently to the RAR. p. 127, 5.4.3 Algae and aquatic plants, Study 2: The EC50 values differ from those given for that study in de RAR. Please correct.				
Dossier Submitter's Response				
We thank DE for their comments. These are addressed below: • p. 121: 72-hr E_bC_{50} for *P. subcapitata*: We agree that the 72-hr E_bC_{50} of 4.5 mg/L listed for this green alga in Table 27 of the CLH Report and again in the study summary at Section 5.4.3 (p. 126) does not match that given in the DAR/RAR or EFSA Conclusion for mesotrione, i.e. 3.5 mg/L. This may be a typo or due to a different way of expressing this endpoint. We have not gone back to check the actual study report (or its subsequent statistical re-analyses) again as the biomass E_bC_{50} endpoint is not in any case used for hazard classification. Its also not now possible to amend the CLH Report. The preferred 72-hr growth rate E_rC_{50} for this species is however identical at 13 mg/L - but this is also much higher than the *Lemna* E_rC_{50} endpoints eventually used for the Acute Aquatic classification (0.0257 - 0.028 mg/L) and any change would not affect the Acute classification proposal. p. 121: 72-hr E_bC_{50} and E_rC_{50} for *N. pelliculosa*: We agree that the 72-hr E_bC_{50} and E_rC_{50} values for this diatom of 68 and 66 mg/L listed in Table 27 of the CLH and again in the study summary at Section 5.4.3 Report (p. 127) do not match those given in the DAR/RAR for mesotrione, i.e. 67 and >96 mg/L respectively. These may be typos or due to a different way of expressing the endpoints. We have not gone back to check the actual study report (or its subsequent statistical re-analyses) again as the biomass E_bC_{50} endpoint is not used for hazard classification and the preferred growth rate E_rC_{50} given in the RAR is higher than that quoted in the CLH. Its also not now possible to amend the CLH Report. The E_rC_{50} endpoint for this species is also much higher than the *Lemna* E_rC_{50} endpoints eventually used for the Acute Aquatic classification (0.0257 - 0.028 mg/L) and any change in the diatom endpoint will not affect the Acute classification proposal.				
RAC's response				
Noted. Thank you for your comment				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	12
Comment received				
Based on the data in the CLH report of mesotrione it can be concluded that the aquatic plant Lemna gibba is the most sensitive species in the aquatic toxicity studies with a 7dErC50=0.028mg/l and a 7dNOErC=0.002mg/l. Together with the fact that the substance is not rapidly degradable it is justified to classify Mesotrione as Aquatic Acute				

1, H400 and Aquatic Chronic 1, H410. The substance does not meet the bioaccumulation criteria. In view of the proposed classification and toxicity band for acute toxicity between 0.01 mg/l and 0.1mg/l, an M-factor for acute toxicity of 10 can be assigned. For chronic toxicity an M-factor of 10 (not rapidly degradable substance and NOEC between 0.001 and 0.01 mg/l) can be set. In conclusion : BE CA agrees with the proposed environmental classification.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted. Thank you for your comment

PUBLIC ATTACHMENTS
1. Mesotrione proposed classification of STOT_RE FINAL.zip [Please refer to comment No. 1, 5, 8]