Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

tribenuron-methyl (ISO); methyl 2-[N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-N-methylcarbamoylsulfamoyl]benzoate

EC Number: 401-190-1
CAS Number: 101200-48-0

CLH-O-0000001412-86-238/F

Adopted

14 September 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TRIBENURON-METHYL (ISO); METHYL 2-[N-(4-METHOXY-6-METHYL-1,3,5-TRIAZIN-2-YL)-N-METHYLCARBAMOYLSULFAMOYL]BENZOATE

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: tribenuron-methyl (ISO); methyl 2-[N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-N-methylcarbamoylsulfamoyl]benzoate
EC number: 401-190-1
CAS number: 101200-48-0
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	1
Comment received				
DuPont kindly submits for consideration by the Risk Assessment Committee (RAC) our reply to the proposed Harmonised Classification and Labelling for Tribenuron Methyl. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf				
Dossier Submitter's Response				
No comment				
RAC's response				
-				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	2
Comment received				
DuPont agrees with the conclusion of the rapporteur that the available data does not provide sufficient evidence for catergory 1B, or as limited evidence for Category 2. Therefore, no classification proposal for carcinogenicity is consistent with the CLP criteria. An increased incidence of mammary gland adenocarcinomas was noted in female rats at excessively high doses, which caused severe body weight reductions greatly exceeding				

the maximum tolerated dose in a strain with a high spontaneous mammary tumor rate. Therefore, this finding has no biological relevance to humans. The specific mechanism(s) involved are not known; however, tribenuron methyl is not genotoxic and as described below does not display estrogen or dopoamine agonist activity. Therefore, the increase in tumors is likely secondary to general toxicity.

DuPont would like to highlight that data examining known modes of action (MoAs) relevant to the induction of mammary tumors by tribenuron methyl are available (summarized in the Tribenuron Methyl RAR Volume 3, Annex B.6, April 2017). The data indicate that tribenuron methyl does not act via an endocrine MoA. To address estrogenic potential , the following in vitro studies have been submitted and evaluated: estrogen receptor binding with rat uterine cytosol (DuPont-45570); estrogen receptor transcriptional activation in HeLa cells (DuPont-45571); and steroidogenesis in human cell line H295R, (DuPont-46408). Negative responses were obtained in each of these studies indicating that tribenuron methyl does not have the potential to interact with the estrogen receptor or impact steroidogenesis.

Furthermore, as part of the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters, in silico/QSAR methods were utilized to assess the potential endocrine activity of tribenuron methyl, (presnted in DuPont-45358; presented and evaluated in Tribenuron Methyl RAR Volume 3, Annex B.6, April 2017). These assessments included estrogenic, androgenic and dopaminergic (agonism and antagonism) activity and utilized the following software programs: OECD QSAR Toolbox v3.3; OASIS TIMES v2.27.16; MedChem Studio v4.0; and ADMET Predictor v7.2. There were no structural alerts for estrogen receptor binding that could be substantiated within the chemical domain (based on results from OECD QSAR Toolbox, the USEPA rtER Expert System ver 1 and the Toolbox Estrogen Receptor Binding alert). Predictons based on OASIS TIMES and ADMET Predictor indicated binding to the estrogen and androgen receptors is unlikely. There are no specific components of the OECD Toolbox or other available software for evaluation of potential dopamine receptor binding. However, in order to better understand the potential for dopamine receptor binding, common pharmacophores were investigated. MedChem Studio v4.0 was used to perform a similarity analysis with tribenuron methyl against known dopamine agonists and antagonists. Not only was there significant structural dissimilarity between tribenuron methyl from the compounds in the dopaminergic data set, but the pKa profiles also differed greatly. Tribenuron methyl lacks a protonated amine at physiological pH, which is a part of a well-known pharmacophore for dopamine receptor binding, and found to exist in all compounds in the dopaminergic data set. The weight of evidence from the results of these evaluations indicates that tribenuron methyl will not bind to dopamine D1, D2 or D3 receptors.

Therefore, the weight of evidence from the in vitro and in silico analyses support that there are no significant concerns with tribenuron methyl for estrogen-, androgen-, or dopamine-mediated activity. The absence of estrogenic and dopamine agonistic activities, the most common MoAs for mammary tumor induction in Sprague-Dawley rats, is consistent with the view that tribenuron methyl is not likely to induce mammary tumors by an endocrine mechanism but by general systemic toxicity due to high doses. Therefore, it is not a relevant risk for humans.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf

Dossier Submitter's Response
No further comment. No classification for carcinogenicity toxicity is proposed by Dossier Submitter.
RAC's response
RAC agrees that no classification for carcinogenicity is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	France		MemberState	3
Comment received				
Page 41: In the 2-year rat toxicity study, a dose-related increased incidence of total mammary gland adenocarcinomas was observed in females. This finding was statistically significant at the highest dose level. The incidences were at the upper limit of the historical control data (range from 8 to 23%) at the mid dose level (22.3%) and twice above the upper limit of the historical control data at the highest dose level (42.6%). Furthermore, the incidence of multiple adenocarcinomas was hugely statistically significantly increased (1 females in the control group vs 11 females in the high dose group). The MoA is unknown. According to the DS, these neoplastic lesions were observed at doses exceeding the MTD, characterized by a decrease in body weight/body weight gains (body weight decreased by 21% and 43% compared to the control group at the mid and high dose levels respectively). However, there was no evidence of overt toxicity at the two highest dose levels since the survival rate was not affected and no increase in clinical observations was observed. Therefore, these dose levels are not considered to be excessive to assess the potential carcinogenicity of tribenuron-methyl. It was also highlighted during the pesticide peer review process that the incidence of C-cell thyroid carcinomas was increased in the male rats of the high dose group. Indeed, as detailed in the updated RAR (April 2017), the incidence of C-cell carcinomas was 1.6% in the control group (1/62) vs 6.6% in the high dose group (4/61), whereas the historical control data showed incidences of 0 to 3.3 %. Therefore, a classification for carcinogenicity in category 2 should be discussed for tribenuron-methyl.				
Dossier Submitter's Response				
Regarding the adenocarcinoma in mammary gland: As 10 % decrease in body weight gain is considered as an adverse effect, a decrease of 21 and 43 % as was the case after exposure of middle and high dose is definitely adverse. It is clear that MTD was exceeded at both these doses. The main toxic effect seen with tribenuron-methyl in all experiments is decrease of body weight. Moreover, the historical control data range from 8 to 26 %. This has been extensively discussed at Pesticide Peer Review Meeting 155 and the majority of the experts agree that the observed tumours at high dose, above the MTD, were not triggering a proposal for classification and labelling. Regarding C-cell thyroid carcinoma: the incidence was slightly outside the laboratory historical control range, but not statistical significant. There is one animal with this cancer in the control group and 4 in the highest dose group (1250 ppm) and no incidence in the low and middle dose group 25 and 250 ppm). Moreover, there is no dose response in the incidence of hyperplasia (a stage before cancer). The incidence in hyperplasia was actually less in the highest dose group (5/61) compared to control (11/62). This has been extensively discussed at Pesticide Peer Review Meeting 155 and the experts considered that the increased incidence of C cells adenoma and carcinoma combined at the HD are not treatment related.				

RAC's response
RAC supports the analysis by the DS and that no classification for carcinogenicity is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	United Kingdom	EU Tribenuron AIR3 Task Force	Company-Manufacturer	4
Comment received				
The Task Force supports the conclusion of the rapporteur that no classification for carcinogenicity is required.				
Dossier Submitter's Response				
No further comment. No classification for carcinogenicity toxicity is proposed by Dossier Submitter.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	5
Comment received				
DuPont agrees with the conclusion of the rapporteur; the results from guideline genotoxicity studies performed with tribenuron methyl were consistently negative. Thus, tribenuron methyl does not meet the classification criteria for germ cell mutagenicity. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf				
Dossier Submitter's Response				
Noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	United Kingdom	EU Tribenuron AIR3 Task Force	Company-Manufacturer	6
Comment received				
The Task Force supports the conclusion of the rapporteur that no classification for mutagenicity is required.				
Dossier Submitter's Response				
No further comment. No classification for mutagenicity is proposed by Dossier Submitter.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	7
Comment received				
DuPont agrees with the conclusion of the rapporteur that no classification for reproductive toxicity is needed. Administration of tribenuron methyl to rats did not have any effect on mating performance or fertility. Offspring toxicity seen as clinical signs, decreased pup weight and organ weight changes occurred in the presence of parental toxicity. In addition, it should be further elaborated that Cat. 1B and Cat. 2 classifications are not warranted based on the presence of severe maternal toxicity in the developmental toxicity studies at doses where resorptions, deaths and skeletal effects were noted in rats, and deaths, nidations, and malformations were noted in rabbits. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf				
Dossier Submitter's Response				
No further comment. No classification for reproductive toxicity is proposed by Dossier Submitter.				
RAC's response				
RAC agrees that no classification for reproductive toxicity is warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	United Kingdom	EU Tribenuron AIR3 Task Force	Company-Manufacturer	8
Comment received				
The Task Force supports the conclusion of the rapporteur that no classification for reproductive toxicity is required.				
Dossier Submitter's Response				
No further comment. No classification for reproductive toxicity is proposed by Dossier Submitter.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	9
Comment received				
DuPont agrees with the rapporteur's assessment that no classification is necessary for acute oral, dermal and inhalation toxicity based on the available data.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf
Dossier Submitter's Response
No further comments. No classification for acute oral, dermal and inhalation toxicity is proposed by Dossier Submitter.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	10
Comment received				
DuPont agrees with the rapporteur's assessment that no classification is necessary for skin irritation based on the available data. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf				
Dossier Submitter's Response				
No further comments. No classification for skin irritation is proposed by Dossier Submitter.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	11
Comment received				
DuPont agrees with the rapporteur's assessment that no classification is necessary for eye irritation based on the available data. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf				
Dossier Submitter's Response				
No further comments. No classification for eye irritation is proposed by Dossier Submitter.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	12
Comment received				
DuPont agrees with the conclusion that tribenuron methyl has a harmonised classification as a skin sensitiser (Skin Sens. 1, H317), and no change to this classification under the CLP criteria is warranted. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf				
Dossier Submitter's Response				
No further comments. Tribenuron-methyl has a harmonised classification as a skin senstiser (Skin Sens. 1, H317). No change is proposed.				
RAC's response				
RAC agrees that the current entry in Annex VI for skin sensitisation is appropriate and that no change is warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Finland		MemberState	13
Comment received				
Two skin sensitisation tests (Buehler method and Guinea Pig Maximization test, OECD 406) conducted with tribenuron-methyl showed positive results. The criteria for classification as Skin Sens. 1; H317 is met. Sufficient data for classification into-subcategories does not exist. FI CA supports the proposal to maintain the current classification of Skin Sens. 1; H317 for tribenuron-methyl.				
Dossier Submitter's Response				
No further comments. Tribenuron-methyl has a harmonised classification as a skin senstiser (Skin Sens. 1, H317). No change is proposed.				
RAC's response				
RAC agrees that the current entry in Annex VI for skin sensitisation is appropriate and that no change is warranted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	14
Comment received				
DuPont agrees with the conclusion of the rapporteur that no classification is proposed for target organs based the available single exposure studies and the lack of irreversible effects observed.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf
Dossier Submitter's Response
No further comments. No classification for STOT SE is proposed by Dossier Submitter.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	15

Comment received

The rapporteur has proposed a classification for STOT RE 2 on the basis of effects observed in a rabbit 28-day dermal study and a rabbit developmental toxicity study as described below:

Classification STOT RE 2, H373 is proposed based on mortalities seen in rabbits at 80 mg/kg bw/day in a developmental toxicity study with 13 days exposure to tribenuron methyl. Furthermore, mortalities and histopathological changes in the kidney (nephrocalcinosis, tubular degeneration/necrosis) were noted in the 28-day rabbit dermal toxicity study using a limit dose level of 1000 mg/kg bw/day.

The rapporteur has noted histopathological changes in the kidneys (nephrocalcinosis, tubular degeneration/necrosis) in both sexes at 1000 mg/kg bw/day in the 28-day dermal toxicity study in rabbits (RAR Vol.3, B.6.3.3.1/01). Furthermore, one male and one female were found dead (on day 29 and day 24, respectively) without clinical signs preceding the death, and no macroscopic abnormalities or microscopic findings were noted that could explain the death. The severity of the observed effect is considered by the rapporteur relevant for a classification as STOT-RE. No NOAEL was determined in this limit dose study. However, the rapporteur noted that the LOAEL of 1000 mg/kg bw/day is close to the higher limit value for the critical range of doses (i.e. 28-day study: 60<C≤600 mg/kg bw/day) for a classification as STOT-RE cat 2.

DuPont does not agree that the data from the 28-day dermal study can be used to support a classification of STOT RE Cat. 2 on the basis that the dose administered in this study is above the higher limit of the critical dose range considered for classification. Further, the study was considered not reliable by the submitter and of "limited relevance" by the rapporteur. Moreover, in the 28-day and 90-day feeding studies in rats, mice, and dogs, which are the studies most relevant for classification, there were no effects justifying target organ toxicity classification based on kidney effects. Therefore, the kidney should not be identified as a target organ for the STOT RE classification.

DuPont agrees that the data from the rabbit developmental study are indicative of morbidity and mortality in the dose range specified in the CLP criteria. Therefore, a classification of STOT RE Cat. 2 may be applicable.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf

Dossier Submitter's Response
The effects noted in the 28-day rabbit study indicate that the kidney might be a target organ in the rabbit. If this data should be considered reliable for classification or not needs to be discussed.
RAC's response
RAC agrees that the effects observed in the 28-day dermal rabbit toxicity study (incl. kidney) are not to be used to support classification. As to the mortality observed in the main rabbit developmental toxicity study, RAC doubts whether this in itself would qualify for classification given the low numbers and unclear relation with treatment. RAC notes however that mortality has also been observed in two pilot rabbit teratogenicity studies, in a dose-related way and at doses falling within/at the upper limit of the extrapolated guidance value range for STOT RE 2. Hence, overall, RAC considers STOT RE 2; H373 warranted for tribenuron-methyl.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	16
Comment received				
DuPont agrees with the key studies relevant for assessing environmental hazards, the endpoints identified for assessing acute and chronic aquatic toxicity, and the conclusions reached on the classification and labeling of tribenuron methyl. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf				
Dossier Submitter's Response				
No further comment				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	France		MemberState	17
Comment received				
FR agrees with the general conclusion dealing with the proposal of classification and M factors for environmental hazard of the substance.				
Dossier Submitter's Response				
No further comment				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	United States	DuPont Crop Protection	Company-Manufacturer	18
Comment received				
DuPont agrees with the rapporteur's assessment of the data and lack of a need for classification based on these data according to the CLP criteria. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf				
Dossier Submitter's Response				
Noted				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. Tribenuron Methyl_Harmonised Classification_DuPont Comments_31Aug 2017.pdf
[Please refer to comment No. 1, 2, 5, 7, 9, 10, 11, 12, 14, 15, 16, 18]