Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

thifensulfuron-methyl (ISO); methyl 3-(4-methoxy-6-methyl- 1,3,5-triazin-2-ylcarbamoylsulfamoyl)thiophene-2-carboxylate

EC Number: -
CAS Number: 79277-27-3

CLH-O-0000001412-86-136/F

Adopted

9 December 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON THIFENSULFURON-METHYL (ISO); METHYL 3-(4-METHOXY-6-METHYL- 1,3,5-TRIAZIN-2-YLCARBAMOYLSULFAMOYL)THIOPHENE-2-CARBOXYLATE

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.

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

Substance name: thifensulfuron-methyl (ISO); methyl 3-(4-methoxy-6-methyl-1,3,5-triazin-2-ylcarbamoylsulfamoyl)thiophene-2-carboxylate
EC number: -
CAS number: 79277-27-3
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2016	Germany		MemberState	1
Comment received				
The German CA supports the proposed harmonised classification as Aquatic Acute 1 and Aquatic Chronic 1 as well as the corresponding M-factors of 100. However, in section 1.1 table 1 of the CLH report the substance name comprises solely the ISO name of the substance ("Thifensulfuron-methyl"). Like in the annex VI entry of the CLP regulation for this substance the IUPAC name "Methyl 3-(4-methoxy-6-methyl-1,3,5-triazin-2-ylcarbamoylsulfamoyl)thiophene-2-carboxy-late" should also be stated section 1.1 table 1 of the CLH report. The CAS name in IUCLID sections 1.1, 1.2 and in part B Table 4 of the CLH report is "2-Thiophenecarboxylis acic, 3-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-, methyl ester". Please correct the typo and replace by "2-Thiophenecarboxylic acid, 3-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-, methyl ester" ECHA note - The following attachment was submitted with the comment above: *DE-MSCA Comments CLH-Thifensulfuron-methyl - Confidental.docx*				
Dossier Submitter's Response				
Thank you for the comments regarding the aquatic classification. The IUPAC name is indicated in table 4 in section 1.1 of Part B. It is considered sufficient to refer to the substance by the ISO name in table 1 in Part A.				

The CAS name in table 4 is 2-Thiophenecarboxylis acid, 3-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-, methyl ester. We are not able to make changes to the IUCLD dossier at this stage.
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Spain		MemberState	2
Comment received				
The Spanish CA supports not classification regarding human health				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Denmark		MemberState	3
Comment received				
DK do not support the proposed non-classification on health of thifensulfuron-methyl. DK support the conclusion reached by EFSA (2015) that thifensulfuron-methyl should be classified Repr. 2, H361d: Suspected of damaging the unborn child. DK also support the EFSA conclusion that the mammary gland tumours in rats could be considered a flag of concern on thifensulfuron-methyl endocrine mediated effect and that the endocrine disruption potential of thifensulfuron-methyl and metabolites cannot be excluded in the absence of further data (e.g. TG 456 – H295R Steroidogenesis Assay).				
Dossier Submitter's Response				
With regard to classification for developmental toxicity, new data recently submitted by DuPont indicate that the original proposal from the DS was appropriate. In a new GLP-compliant rat developmental toxicity study, animals (22/group) were dosed from gestation day (GD) 6 until GD 20 (in compliance with modern guidelines) at 0 and 800 mg/kg bw/d (the dose level at which the findings of absent/small renal papilla were seen in the original study) and kidney and renal papilla of foetuses were examined at GD 21 (instead of GD 20, as in the preceding study). In addition, external examinations of the foetuses were performed. No abnormalities of the kidney or renal pelvis were found. There was no evidence of microphthalmia. In addition, an estimation (using data from the available kinetic studies) of systemic blood exposure at GD19 (start of development of renal papilla in rats) comparing the original developmental toxicity study and the multigeneration study shows that in the developmental toxicity study, since dosing had ceased at GD15, the systemic blood concentration of thifensulfuron methyl at the top dose of 800 mg/kg bw/d in pregnant dams had decreased to about 0.48 µg/mL by GD19. In contrast, in the multigeneration study with continuous dietary exposure, the systemic blood concentration at GD19 (and subsequently) at the top dose of 244 mg/kg bw/d in females had been maintained at approximately 10-fold higher (4.4 µg/mL). There were no histopathological changes in the				

kidneys from second generation weanlings in the multigeneration reproduction study despite the higher systemic blood exposure.
These new data support the position of the CLH report that the distribution of renal pelvic findings in the original developmental study is not abnormal, and represents a chance distribution of normal stages of renal development, for which no classification is appropriate.

With regard to the mammary gland tumours, new data on a possible endocrine MoA submitted by DuPont indicate:

- absence of estrogenic or anti-estrogenic activity of thifensulfuron-methyl as shown by multiple published EPA ToxCast high-throughput screening assays;
  - absence of interaction with estrogen and dopamine receptors of thifensulfuron-methyl, as shown by QSAR;
  - absence of interaction with the dopamine receptor of thifensulfuron-methyl in a receptor binding assay;
  - absence of estrogenic activity of thifensulfuron-methyl in-vivo (uterotrophic assay);
  - absence of effect on prolactin secretion of thifensulfuron-methyl in-vivo;
  - absence of estrogenic activity of the metabolite IN-A4098 (triazine amine), both in an in-vitro receptor binding assay and by QSAR.

These new data investigate the principal known endocrine activities by which chemicals might affect mammary tumour incidence. The results strongly show that thifensulfuron methyl influences no endocrine tumorigenic MoA in the rat, and that the observed minor differences in tumour incidence are entirely incidental. Thifensulfuron methyl shows no endocrine activity.

RAC's response

Noted. A discussion on ED properties is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
13.04.2016	Netherlands		MemberState	4

Comment received

The Dutch CA supports the proposed environmental classification of thifensulfuron-methyl as
Aquatic Acute 1 (H400) with M-factor = 100 and Aquatic Chronic 1 (410) with M-factor 100.

Dossier Submitter's Response

Thank you.

RAC's response

Thank you.

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2016	United States	DuPont Crop Protection	Company-Manufacturer	5

Comment received

Submission of Report 8 out of 8 Confidential Reports.

ECHA note - The following attachment was submitted with the comment above:

DuPont-44802 -Thifensulfuron methyl technical developmental reproductibility toxicity in rats.zip
Dossier Submitter's Response
Thank you. A summary of these new data will be included in the DS response to some of the comments received, where appropriate.
RAC's response
Thank you.

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2016	United States	DuPont Crop Protection	Company-Manufacturer	6
Comment received				
DuPont Crop Protection (DuPont) supports the proposal to not "classify for any human health hazard classes" as concluded in the CLH report for thifensulfuron-methyl (March 2016) prepared by the United Kingdom, the Rapporteur Member State. The additional evaluations and new data presented confirm that the requirements for carcinogenicity and developmental toxicity (based on observations in the rat developmental toxicity study) classifications under Regulation (EC) 1272/2008 have not been met. It also supports the conclusion that observed distribution of mammary tumours in the 2-year rat study are neither related to thifensulfuron-methyl administration nor are associated with an endocrine-mediated mode-of-action. The file size for the confidential reports was inadequate for the 8 confidential reports. Therefore, the 8 confidential will be submitted directly to the RMS. ECHA note - The following attachments were submitted with the comment above: *DuPont Confidential Reports (7).zip* *Public Consultation of Thifensulfuron-methyl.pdf*				
Dossier Submitter's Response				
Thank you. A summary of these new data will be included in the DS response to some of the comments received, where appropriate.				
RAC's response				
Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	Belgium		Individual	7
Comment received				
A particular attention should be paid on the minimum degree of purity indicated for thifensulfuron-methyl to identify the active substance. The reference minimum purity which is going be included in the final act and related final review report issued by the European Commission will result from further legal and technical considerations. Indeed, there is still discussion on the need to amend the minimum purity of the active substance with strong recommendation that the minimum purity of thifensulfuron-methyl should not be changed and should remain at 960 g/kg.				
Dossier Submitter's Response				
We agree – the minimum purity should be set at 960 g/kg.				

RAC's response
Thank you. Agreed

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2016	United States	DuPont Crop Protection	Company-Manufacturer	8
Comment received				
Re-submission of the non-confidential position paper is made, since it hasn't been posted and therefore, DuPont is uncertain if it has been received. ECHA note - The following attachment was submitted with the comment above: *Public Consultation of Thifensulfuron-methyl.pdf*				
Dossier Submitter's Response				
Thank you. A summary of these new data will be included in the DS response to some of the comments received, where appropriate.				
RAC's response				
Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	France	Rotam Agrochemical Europe Ltd.	Company-Manufacturer	9
Comment received				
Comment No. 1 : A particular attention should be paid on the minimum degree of purity indicated for thifensulfuron-methyl to identify the active substance. The reference minimum purity which is going be included in the final act and related final review report issued by the European Commission will result from further legal and technical considerations. Indeed, there is still discussion on the need to amend the minimum purity of the active substance with strong recommendation that the minimum purity of thifensulfuron-methyl should not be changed and should remain at 960 g/kg. Comment No. 2 : Rotam Agrochemical Europe supports the proposal to not "classify for any human health hazard classes" as concluded in the CLH report for thifensulfuron-methyl (March 2016) prepared by the United Kingdom, the Rapporteur Member State. The additional evaluations and new data presented by the main notifier DuPont confirm that the requirements for carcinogenicity and developmental toxicity (based on observations in the rat developmental toxicity study) classifications under Regulation (EC) 1272/2008 have not been met. It also supports the conclusion that observed distribution of mammary tumours in the 2-year rat study are neither related to thifensulfuron-methyl administration nor are associated with an endocrine-mediated mode-of-action.				
Dossier Submitter's Response				
We agree – the minimum purity should be set at 960 g/kg. A summary of the new data will be included in the DS response to some of the comments received, where appropriate.				
RAC's response				
Thank you. Agreed				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Netherlands		MemberState	10
Comment received				
In table 11 on page 26, only the incidence of tumours for female rats is reported. It would be very helpful for the interpretation of the results if the same was reported for the male rats (as is done in the RAR). TSM was not found to be carcinogenic in an 18-month mouse carcinogenicity study. Also in rats there is not sufficient evidence for carcinogenicity. A trend towards increased mammary gland adenocarcinoma in female rats (29% and 32% at 500 and 2500 ppm respectively vs 21% in controls, not statistically significant) was observed. At the top-dose, this is a 1.5-fold increase compared to the controls without reduction in latency; similar tumours were not seen in the mouse. The incidence of mammary gland hyperplasia and adenoma was high but comparable in all groups. Taken together, we agree that no classification for carcinogenicity is warranted.				
Dossier Submitter's Response				
Thank you for your support. All data relevant to the classification of thifensulfuron methyl has been included in the CLH dossier. The incidence of tumours in male rats was not considered relevant but can be viewed from the RAR.				
RAC's response				
Noted. A discussion on carcinogenicity is done in the ODD				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Spain		MemberState	11
Comment received				
We agreed with the dossier submitter that there is insufficient evidence for classification. Although the increased incidences for mammary adenocarcinoma of 29% and 32% observed at 500 and 2500 ppm respectively in female Sprague-Dawley rats were slightly above the laboratory HCD (range = 8.3-23.4%), they were within contemporary published HCD (range =7-31%). Besides, these incidences were not even two-fold than that in the concurrent controls (21%); were not statistically significantly different from that in controls; were not clearly dose-related; tumour latency was not shortened compared to the latency of the same tumours seen in controls and similar tumours were not seen in the mouse study. The CLP Guidance document, version 4.1 of June 2015 (carcinogenicity section) specifies that female Sprague-Dawley rats have a high spontaneous incidence of mammary gland tumours by referring to a publication by the NTP (2005). This support the conclusion that these tumours are not treatment-related but more likely chance findings in a strain of rats highly susceptible to mammary gland tumourigenesis, part of normal biological variability. In addition, new data generated to investigate the principal known endocrine activities by which thifensulfuron methyl might affect mammary tumour incidence demonstrate that, thifensulfuron methyl influences no endocrine tumorigenic MoA in the rat. It shows no endocrine activity and that the observed minor differences in tumour incidence are entirely incidental.				

No classification was also proposed by the TCC&L group of the EU in 1997 on the basis of the same data. EFSA, during the renewal peer-review process, concluded that although classification for carcinogenicity was not warranted, it could not be excluded that the increase in mammary tumours seen in the rat carcinogenicity study was treatment-related.

The Spanish position, based in the whole data, is that classification regarding carcinogenicity is not required.

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

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Denmark		MemberState	12

Comment received

An increase in mammary gland tumours have been observed in a two year rat study (Sprague Dawley). These incidences are above the concurrent control and the relevant historical control at 500 ppm and 2500 ppm. DK would not exclude mammary gland tumours in rats as being treatment-related and it could be considered a flag of concern on thifensulfuron-methyl endocrine mediated effect.
DK does not consider comparison with other published control data relevant as otherwise suggested in the CLH report page 28.
Endocrine disruption-sensitive parameters were not investigated in the two generation study performed on the substance as it is an old version of the Test guideline (OECD TG 416). Furthermore there are no mechanistic data to clearly exclude the potential interaction of thifensulfuron-methyl and metabolites with hormone receptors. The CLH report mentions QSAR and an in vitro E-screen assay page 29. However, the endocrine disruption potential cannot be excluded in the absence of further data (e.g. TG 456-H295R Steroidogenesis Assay).
Worth noticing is:
Tribenuron-methyl, another triazinsulfonylurea herbicide, has also shown mammary gland tumours and mechanistic data indicate a potential interaction with hormone receptors (EFSA Scientific Report (2004) 15, 1-52, Conclusion on the peer review of tribenuron, page 12)
Triasulfuron, another sulfonylurea pesticide, has also shown tumours in mammary glands and a possible endocrine mode of action have not been clarified (EFSA Technical report 2015, Assessment of endocrine disrupting properties in EFSA Conclusions on the Pesticides Peer Review, page 21)

Dossier Submitter's Response

The DS reiterates that classification for carcinogenicity is not appropriate for the following reasons:
mammary tumours are common in S-D female rats;
- the perceived increase in the incidence of mammary tumours is small, is not statistically significant, and there is no clear dose-response;
- tumour latency was not decreased;
- when additional sources of historical control data using the same strain, same breeder

and same diet are included, the "higher" incidence is shown to be within the published historical control range;
- high incidences of mammary gland hyperplasia (a precursor lesion to mammary neoplasia) were seen in all groups, with the highest incidence (97%) in controls.

Furthermore, new data on a possible endocrine MoA submitted by DuPont indicate:

- absence of estrogenic or anti-estrogenic activity of thifensulfuron-methyl as shown by multiple published EPA ToxCast high-throughput screening assays;
- absence of interaction with estrogen and dopamine receptors of thifensulfuron-methyl, as shown by QSAR;
- absence of interaction with the dopamine receptor of thifensulfuron-methyl in a receptor binding assay;
- absence of estrogenic activity of thifensulfuron-methyl in-vivo (uterotrophic assay);
- absence of effect on prolactin secretion of thifensulfuron-methyl in-vivo;
- absence of estrogenic activity of the metabolite IN-A4098 (triazine amine), both in an in-vitro receptor binding assay and by QSAR.

These new data investigate the principal known endocrine activities by which chemicals might affect mammary tumour incidence. The results strongly show that thifensulfuron methyl influences no endocrine tumorigenic MoA in the rat, and that the observed minor differences in tumour incidence between treated groups and controls are entirely incidental. Thifensulfuron methyl shows no endocrine activity.

During the peer-review process, EFSA suggested a possible link between mammary tumour incidences reported with thifensulfuron-methyl and tribenuron-methyl. EFSA suggested that the mammary tumour response seen in Sprague-Dawley rats with thifensulfuron-methyl represented a common feature among triazinyl-sulfonylurea active substances. An increased mammary tumour incidence was observed in Sprague-Dawley rats with tribenuron-methyl but only at doses exceeding the MTD (EFSA, 2004). In relation to tribenuron-methyl, EFSA therefore concluded "the carcinogenic effect in female rats was not considered to be of sufficient evidence for classification of tribenuron-methyl as a carcinogen".

In the new data provided by DuPont, an evaluation of publically available toxicological reviews of 10 triazinyl-sulfonylurea active substances (including thifensulfuron-methyl and tribenuron-methyl) did not demonstrate a pattern of mammary tumour induction (see table below). Chronic studies with most of these active substances utilized the Sprague-Dawley rat strain, which is well-known for its high spontaneous mammary tumour incidence rate. With the exception of tribenuron-methyl, any mammary tumour incidences were confirmed to be within the background variability for this strain; and even tribenuron-methyl was not classified for carcinogenicity (ECHA, 2013). Furthermore, the absence of correlation in mammary tumour incidences between metsulfuron-methyl, tribenuron-methyl, chlorsulfuron-methyl, and thifensulfuron-methyl, which all produce the common triazine metabolite IN-A4098, demonstrate that IN-A4098 is unlikely to be associated with the induction of mammary gland tumours.

Summary of carcinogenic effects observed with triazinyl-sulfonylureas

Active substance	Tumour Response[a]	Reference
Chlorsulfuron-methyl	Not carcinogenic[b]	ECHA, 2014
Ethametsulfuron-methyl	Not carcinogenic	EFSA, 2014
Iodosulfuron	Not carcinogenic	EU Commission, 2003
Metsulfuron-methyl	Not carcinogenic	EFSA, 2015a

Prosulfuron	Not carcinogenic	EU Commission, 2013a
Thifensulfuron-methyl	Not carcinogenic[c]	UK CRD, 2015b
Triasulfuron	Not carcinogenic	EU Commission, 2013b; EFSA, 2015b
Tribenuron-methyl	Not carcinogenic[d]	EFSA, 2004
Triflusulfuron-methyl	Proposed C2 under CLP[e]	EFSA, 2008b
Tritosulfuron	Not carcinogenic[f]	Germany, 2002

[a] Test substance related tumours, outside of the historical control range;
[b] Slight increase in Leydig cell tumours which did not result in classification;
[c] Non-carcinogenic according to existing classification. No classification proposed in the EFSA Conclusion (EFSA, 2015c);
[d] Increased rat mammary tumours at doses exceeding the MTD – considered insufficient for classification;
[e] Classification proposal based on increased Leydig cell tumour incidence with aromatase inhibition considered to be the MoA;
[f] Tritosulfuron containing <0.02% of the process impurity AMTT was considered to be non-carcinogenic.

RAC's response

Noted. A discussion on carcinogenicity is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	Belgium		Individual	13

Comment received

FMC chemical sprl(Cheminova AS) fully supports "no classification" for carcinogenicity, as proposed in the CLH report.
EFSA concluded that mammary tumours might be treatment-related due to a perceived incidence (at the top dose) outside the historical control range; and therefore EFSA also concluded that endocrine activity cannot be ruled out.
The CLH report adequately details that:
- mammary tumours are common in female rats of this strain
- the perceived increase in the incidence of mammary tumours is small, is not statistically significant, and no clear association with dose is present
- an estimation of systemic exposure suggests a clear dose-response could be expected if a tumorigenic effect was indeed present
- tumour latency was not decreased
- when additional sources of historical control data using the same strain, same breeder and same diet are included, the "higher" incidence is shown to be within the historical control range
- high incidences of mammary gland hyperplasia (a precursor lesion to mammary neoplasia) were seen in all groups, with the highest incidence (97%) in controls.
Some additional new studies were however performed which further support that there is no underlying endocrine Mode of Action (MoA). These new data are:
- absence of estrogenic or anti-estrogenic activity as shown by multiple published EPA ToxCast high-throughout screening assays
- absence of interaction with estrogen and dopamine receptors, as shown by QSAR
- absence of interaction with the dopamine receptor in a receptor binding assay
- absence of estrogenic activity in-vivo (uterotrophic assay)
- absence of effect on prolactin secretion in-vivo
- absence of estrogenic activity of the metabolite IN-A4098, both in an in-vitro receptor binding assay and by QSAR.
These new data investigate the principal known endocrine activities by which chemicals might affect mammary tumour incidence. The results strongly support that thifensulfuron methyl influences no endocrine tumorigenic MoA in the rat, and that the observed minor

differences in tumour incidence are entirely incidental. Thifensulfuron methyl shows no endocrine activity.
Reports for each of these studies were already submitted by an other organisation as confidential data.
Comments offered by other commentators during the 2015 EFSA review suggested that mammary tumours might be due to similarity to atrazine, or might be a common property of triazinyl sulfonylureas. These comments are not addressed in the CLH report. Data are therefore submitted to demonstrate that:
- thifensulfuron methyl has no structural or functional similarity to atrazine
- mammary tumours are not a common property of the triazinyl sulfonylureas

Dossier Submitter's Response

Thank you for your comments. A summary of the new data will be included in the DS response to some of the comments received, where appropriate.

With regard to a possible similarity between thifensulfuron methyl and atrazine (a chloro triazine herbicide known to cause an increase in mammary tumours), data submitted by DuPont indicate that there are important differences in chemical structure and biological activity between these two substances and their metabolites. The herbicidal mode of action for thifensulfuron-methyl (acetolactate synthase inhibitor) differs from that for atrazine (Photosystem II inhibitor). The triazine metabolite of thifensulfuron-methyl (IN-A4098) also differs in structure from the triazine metabolite of atrazine and is not herbicidally active. Furthermore, in studies with atrazine, tumour latency was demonstrated to be decreased (Eldridge et al, 1999), whereas, tumour latency was not decreased in the case of thifensulfuron-methyl (CLH dossier, UK CRD 2016). Atrazine caused a dose-dependent decrease in prolactin release (Cooper et al, 2007), whereas no effects on serum prolactin levels were observed in rats administered thifensulfuron-methyl (DuPont 2015b). These observations demonstrate that the apparent slight increase in mammary tumours in Sprague-Dawley rats administered thifensulfuron-methyl is not related to the atrazine mode of action.

RAC's response

Noted. A discussion on carcinogenicity is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2016	United States	DuPont Crop Protection	Company-Manufacturer	14

Comment received

DuPont Crop Protection (DuPont) supports the proposal for "no classification" for carcinogenicity as proposed in the CLH report for thifensulfuron methyl (March 2016) prepared by the United Kingdom, the Rapporteur Member State.
The conclusion that thifensulfuron methyl should not be classified for carcinogenicity, and that the increase in mammary tumours is due to the high spontaneous background incidence in the species and strain, is supported by new data generated according to the OECD Conceptual Framework (OECD, 2012). These new data demonstrate:- absence of estrogenic or anti-estrogenic activity as shown by multiple published EPA ToxCast high-throughput screening assays
- absence of interaction with estrogen and dopamine receptors, as shown by QSAR
- absence of interaction with the dopamine receptor in a receptor binding assay
- absence of estrogenic activity in-vivo (uterotrophic assay)

- absence of effect on prolactin secretion in-vivo
- absence of estrogenic activity of the metabolite IN-A4098, both in an in-vitro receptor binding assay and by QSAR.

These new data investigate the principal known endocrine activities by which chemicals might affect mammary tumour incidence. The results strongly support that thifensulfuron methyl influences no endocrine tumorigenic MoA in the rat, and that the observed minor differences in tumour incidence are entirely incidental. Thifensulfuron methyl shows no endocrine activity.

Reports for each of these studies are submitted as confidential data.

The CLH report adequately details that:

- mammary tumours are common in female rats of this strain
- the perceived increase in the incidence of mammary tumours is small, is not statistically significant, and no clear association with dose is present
- an estimation of systemic exposure suggests a clear dose-response could be expected if a tumorigenic effect was indeed present
- tumour latency was not decreased
- when additional sources of historical control data using the same strain, same breeder and same diet are included, the "higher" incidence is shown to be within the historical control range
- high incidences of mammary gland hyperplasia (a precursor lesion to mammary neoplasia) were seen in all groups, with the highest incidence (97%) in controls.

Comments offered by other commentators during the 2015 EFSA review suggested that mammary tumours might be due to similarity to atrazine, or might be a common property of triazinyl sulfonylureas. These comments are not addressed in the CLH report. Data are therefore submitted to demonstrate that:

- thifensulfuron methyl has no structural or functional similarity to atrazine
- mammary tumours are not a common property of the triazinyl sulfonylureas.

ECHA note - The following attachments were submitted with the comment above:
DuPont Confidential Reports (7).zip
Public Consultation of Thifensulfuron-methyl.pdf

Dossier Submitter's Response

Thank you for your comments. A summary of the new data will be included in the DS response to some of the comments received, where appropriate.

RAC's response

Noted. A discussion on carcinogenicity is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	France	Rotam Agrochemical Europe Ltd.	Company-Manufacturer	15

Comment received

Rotam Agrochemical Europe supports the proposal for "no classification" for carcinogenicity as proposed in the CLH report for thifensulfuron methyl (March 2016) prepared by the United Kingdom, the Rapporteur Member State. The conclusion that thifensulfuron methyl should not be classified for carcinogenicity, and that the increase in mammary tumours is due to the high spontaneous background incidence in the species and strain, is supported by new data generated according to the OECD Conceptual

Framework (OECD, 2012). These new data demonstrate: - absence of estrogenic or anti-estrogenic activity as shown by multiple published EPA ToxCast high-throughput screening assays - absence of interaction with estrogen and dopamine receptors, as shown by QSAR - absence of interaction with the dopamine receptor in a receptor binding assay - absence of estrogenic activity in-vivo (uterotrophic assay) - absence of effect on prolactin secretion in-vivo - absence of estrogenic activity of the metabolite IN-A4098, both in an in-vitro receptor binding assay and by QSAR. These new data investigate the principal known endocrine activities by which chemicals might affect mammary tumour incidence. The results strongly support that thifensulfuron-methyl influences no endocrine tumorigenic MoA in the rat, and that the observed minor differences in tumour incidence are entirely incidental. Thifensulfuron-methyl shows no endocrine activity. The CLH report adequately details that: - mammary tumours are common in female rats of this strain - the perceived increase in the incidence of mammary tumours is small, is not statistically significant, and no clear association with dose is present - an estimation of systemic exposure suggests a clear dose-response could be expected if a tumorigenic effect was indeed present - tumour latency was not decreased - when additional sources of historical control data using the same strain, same breeder and same diet are included, the "higher" incidence is shown to be within the historical control range - high incidences of mammary gland hyperplasia (a precursor lesion to mammary neoplasia) were seen in all groups, with the highest incidence (97%) in controls. Comments offered by other commentators during the 2015 EFSA review suggested that mammary tumours might be due to similarity to atrazine, or might be a common property of triazinyl sulfonylureas. These comments are not addressed in the CLH report. Data are therefore submitted by the main notifier to demonstrate that: - thifensulfuron-methyl has no structural or functional similarity to atrazine - mammary tumours are not a common property of the triazinyl sulfonylureas.
Dossier Submitter's Response
Thank you for your comments. A summary of the new data will be included in the DS response to some of the comments received, where appropriate.
RAC's response
Noted. A discussion on carcinogenicity is done in the ODD

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Netherlands		MemberState	16
Comment received				
For the sake of completeness, on page 25, it would be good to add that no clear conclusions could be drawn about the potential of TSM to cause gene mutations in bacteria due its bacteriostatic nature (as is described on page 24). Given the other				

negative study results, we do support no classification.
Dossier Submitter's Response
Thank you for your support for no classification for mutagenicity. We note your comments but the CLH report cannot be updated at this stage.
RAC's response
Noted. A discussion on genotoxicity is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	Belgium		Individual	17
Comment received				
FMC Chemical sprl (Cheminova AS) fully supports "no classification" for mutagenicity.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Thank you				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Sweden		MemberState	18
Comment received				
Based on the arguments presented regarding germ cell mutagenicity, the Swedish CA supports that the available information does not meet the requirements of the CLP criteria for classification of thifensulfuron-methyl (CAS No. 79277-27-3) as a germ cell mutagen. Accordingly, classification for germ cell mutagenicity is not warranted. We would also like to take the opportunity to comment that the results of the studies are merely presented as concluding statements, for example negative or no effect, without reporting any data. For that reason it is not possible for the reader to evaluate the studies thoroughly and to judge if the conclusion made by the DS is acceptable. A higher level of detail is indeed desirable				
Dossier Submitter's Response				
Thank you for your support. All the information relevant to the classification of thifensulfuron methyl has been included in the CLH report. Further details of studies can be found in the RAR, if required. We are not able to update the CLH report at this stage.				
RAC's response				
Noted. A discussion on genotoxicity is done in the ODD				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Spain		MemberState	19

Comment received
We agree with the dossier submitter that the observed developmental toxicity (delayed development of the renal papilla, delayed ossification and reduced foetal weight) appeared to be the consequence of retardation and was seen in the presence of some maternal toxicity. It is most likely the unspecific, secondary consequence of the maternal toxicity observed. No classification was also proposed by the TCC&L group of the EU in 1997 on the basis of the same data. EFSA, during the renewal peer-review process, concluded that classification with Repr. Cat 2; H361d was appropriated (based on the same data available at the time of the first review). In our opinion, no classification is required.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted. A discussion on the toxicity to reproduction data is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
15.04.2016	France		Individual	20
Comment received				
Developmental toxicity p. 34-39 Increased incidence of absent renal papilla was observed in 5 foetuses from 5 litters at the dose level of 800 mg/kg bw/d in the rat developmental toxicity study. This incidence is clearly above the laboratory historical control data (max. 3 foetuses from 3 litters). It is acknowledged that the method for examining renal papilla development has evolved since the study was performed; nevertheless, it seems that the same method was applied in the study conducted on thifensulfuron-methyl and in the studies from which the laboratory historical control data were obtained. Therefore, the available laboratory historical control data are considered relevant. Moreover, the maternal toxicity observed at this dose level is not considered sufficiently severe to induce such effects in the foetuses, taking also into account that the decreased in foetal body weight is slight in this group (3% compared to control group). Furthermore, the absence of renal papilla was considered as a malformation by the study author and is considered as a "grey zone" anomaly in the DevTox database. It should also be noted that statistically significant increased incidence of small renal papilla was observed in this study and supported the evidence for a developmental effect related to thifensulfuron-methyl administration. As a conclusion, it cannot be excluded that findings in renal papilla were not treatment-related and a classification Repr Cat 2 H361d is proposed for thifensulfuron-methyl.				
Dossier Submitter's Response				
Thank you for your comments and for your concerns. However, please note that new data recently submitted by DuPont indicate that the original proposal from the DS (no classification for developmental toxicity) was appropriate. In a new GLP-compliant rat developmental toxicity study, animals (22/group) were dosed from gestation day (GD) 6 until GD 20 (in compliance with modern guidelines) at 0 and 800 mg/kg bw/d (the dose level at which the findings of absent/small renal papilla were seen in the original study) and kidney and renal papilla of foetuses were examined at GD 21 (instead of GD 20, as in				

the preceding study). In addition, external examinations of the foetuses were performed. No abnormalities of the kidney or renal pelvis were found. There was no evidence of microphthalmia.

In addition, an estimation (using data from the available kinetic studies) of systemic blood exposure at GD19 (start of development of renal papilla in rats) comparing the original developmental toxicity study and the multigeneration study shows that in the developmental toxicity study, since dosing had ceased at GD15, the systemic blood concentration of thifensulfuron methyl at the top dose of 800 mg/kg bw/d in pregnant dams had decreased to about 0.48 µg/mL by GD19. In contrast, in the multigeneration study with continuous dietary exposure, the systemic blood concentration at GD19 (and subsequently) at the top dose of 244 mg/kg bw/d in females had been maintained at approximately 10-fold higher (4.4 µg/mL). There were no histopathological changes in the kidneys from second generation weanlings in the multigeneration reproduction study despite the higher systemic blood exposure.

These new data support the position of the CLH report that the distribution of renal pelvic findings in the original developmental study is not abnormal, and represents a chance distribution of normal stages of renal development, for which no classification is appropriate.

RAC's response
Noted. A discussion on the toxicity to reproduction data is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Denmark		MemberState	21

Comment received

The findings in the rat fetuses from the prenatal developmental toxicity study (OECD TG 414) are signs of delayed development (of kidney). The findings are not regarded as secondary to the limited maternal toxicity (decrease in body weight gain (11% non-significant)) and cannot be excluded to be treatment related.
At 800 mg/kg bw/d, the macroscopic observation of size 0 (absent renal papilla) was recorded in 5 fetuses which was above the study control and also above the laboratory historical control data of 0/0-3/3 (from 1980-1989). The historical control data were also performed with macroscopically evaluation. Hence, these data could be used for comparison and the argumentation of reassigning the observations from size 0 to size 1 due to lack of microscopically confirmation is not relevant (CLH report page 35).
The effects resulting in delayed development cannot be excluded to be treatment related. It is a sign of interference with normal development of the conceptus due to prenatal exposure.
Hence, classification with Repr. 2, H361d: 'Suspected of damaging the unborn child' is warranted.

Dossier Submitter's Response

Thank you for your comments and for your concerns. However, please note that new data recently submitted by DuPont indicate that the original proposal from the DS (no classification for developmental toxicity) was appropriate. In a new GLP-compliant rat developmental toxicity study, animals (22/group) were dosed from gestation day (GD) 6 until GD 20 (in compliance with modern guidelines) at 0 and 800 mg/kg bw/d (the dose level at which the findings of absent/small renal papilla were seen in the original study)

and kidney and renal papilla of foetuses were examined at GD 21 (instead of GD 20, as in the preceding study). In addition, external examinations of the foetuses were performed. No abnormalities of the kidney or renal pelvis were found. There was no evidence of microphthalmia.

In addition, an estimation (using data from the available kinetic studies) of systemic blood exposure at GD19 (start of development of renal papilla in rats) comparing the original developmental toxicity study and the multigeneration study shows that in the developmental toxicity study, since dosing had ceased at GD15, the systemic blood concentration of thifensulfuron methyl at the top dose of 800 mg/kg bw/d in pregnant dams had decreased to about 0.48 µg/mL by GD19. In contrast, in the multigeneration study with continuous dietary exposure, the systemic blood concentration at GD19 (and subsequently) at the top dose of 244 mg/kg bw/d in females had been maintained at approximately 10-fold higher (4.4 µg/mL). There were no histopathological changes in the kidneys from second generation weanlings in the multigeneration reproduction study despite the higher systemic blood exposure.

These new data support the position of the CLH report that the distribution of renal pelvic findings in the original developmental study is not abnormal, and represents a chance distribution of normal stages of renal development, for which no classification is appropriate.

RAC's response

Noted. A discussion on the toxicity to reproduction data is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Netherlands		MemberState	22

Comment received

In rats, TSM caused limited maternal toxicity (small decrease in body weight gain) and some degree of developmental toxicity; increased absence of the renal papilla, delayed ossification and reduced foetal weight at the top dose level of 800 mg/kg bw/day.

The only developmental concern is the small increase in absent renal papilla in the rat study at the highest dose. Although it is not significant, it is outside the HC range of the performing laboratory. The provided information states that the papilla develops during the last pre-natal days and that absent papilla can develop normally. Therefore, this could be considered a variation. However, exposure to some substances like methyl salicylate may result in persistent effects. Differentiation between reversible and persistent kidney effects is not possible at birth and therefore also not before birth (Woo and Hoar, 1972). This would require anatomic studies of the neonate and weanling. Absence of renal papilla was considered a malformation according to a group of experts (Solecki, 2003). The CLH proposals contains an error in the calculation of the litter incidence 5/25 = 20% and not 2% which has consequences for the argumentation. As there is an increase outside the HC of the performing lab of an effect for which it is unclear whether it is a variation or malformation in the presence of minimal maternal toxicity, classification in Cat 2 is warranted.

However, if the new study provided on the developmental toxicity in the rat by Dupont shows no effect on the developing kidney and this is confirmed by the dossier submitter than we would agree with no classification seen the limitations of the old developmental study (only macroscopic observations) and the small increase in incidence of absent renal

papilla in this study.
Dossier Submitter's Response
Thank you for your comments and for your concerns. However, please note that new data recently submitted by DuPont indicate that the original proposal from the DS (no classification for developmental toxicity) was appropriate. In a new GLP-compliant rat developmental toxicity study, animals (22/group) were dosed from gestation day (GD) 6 until GD 20 (in compliance with modern guidelines) at 0 and 800 mg/kg bw/d (the dose level at which the findings of absent/small renal papilla were seen in the original study) and kidney and renal papilla of foetuses were examined at GD 21 (instead of GD 20, as in the preceding study). In addition, external examinations of the foetuses were performed. No abnormalities of the kidney or renal pelvis were found. There was no evidence of microphthalmia. In addition, an estimation (using data from the available kinetic studies) of systemic blood exposure at GD19 (start of development of renal papilla in rats) comparing the original developmental toxicity study and the multigeneration study shows that in the developmental toxicity study, since dosing had ceased at GD15, the systemic blood concentration of thifensulfuron methyl at the top dose of 800 mg/kg bw/d in pregnant dams had decreased to about 0.48 µg/mL by GD19. In contrast, in the multigeneration study with continuous dietary exposure, the systemic blood concentration at GD19 (and subsequently) at the top dose of 244 mg/kg bw/d in females had been maintained at approximately 10-fold higher (4.4 µg/mL). There were no histopathological changes in the kidneys from second generation weanlings in the multigeneration reproduction study despite the higher systemic blood exposure. These new data support the position of the CLH report that the distribution of renal pelvic findings in the original developmental study is not abnormal, and represents a chance distribution of normal stages of renal development, for which no classification is appropriate.
RAC's response
Noted. A discussion on the toxicity to reproduction data is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2016	United States	DuPont Crop Protection	Company-Manufacturer	23
Comment received				
DuPont Crop Protection (DuPont) supports the proposal for "no classification" for reproductive toxicity" as proposed in the CLH report for thifensulfuron methyl (March 2016) prepared by the United Kingdom, the Rapporteur Member State. As new data to support "no classification"' DuPont submits a new developmental toxicity study in rats, specifically targeted to examine the renal papilla (source of uncertainty in the first study as described in the CLH report). In the new GLP-compliant study, animals were dosed from gestation day (GD) 6 until GD 20 (in compliance with modern guidelines) and kidney and renal papilla of foetuses were examined at GD 21 (instead of GD 20, as in the preceding study). No abnormalities of the kidney or renal pelvis were found. In addition, an estimation of systemic exposure comparing the original developmental toxicity study and the multigeneration study, both estimated at GD19, is provided				

(DuPont-45278). The significance of GD19 is that this is approximately the start of development of the renal papilla in rats. In the developmental toxicity study, since dosing ceased at GD15,the systemic blood concentration of thifensulfuron methyl in pregnant dams would have decreased to about 0.48 µg/mL by GD19. In contrast, in the multigeneration study with continuous dietary exposure, the systemic blood concentration at GD19 (and subsequently) would have been maintained at approximately 10-fold higher (4.4 µg/mL). If dose-related changes in the renal papilla were truly dose-related, they would therefore have been expected to be more evident in the multigeneration study than the previous developmental study. This is supported by the absence of histopathological changes in the kidneys from second generation weanlings in the multigeneration reproduction study.
These new data support DuPont's position and the position of the CLH report that the distribution of renal pelvic findings in the original study is not abnormal, and represents a chance distribution of normal stages of renal development, for which no classification is appropriate. There is no evidence that the development of renal papilla was abnormal in any way.
The new developmental toxicity study (DuPont-44802) and the study describing systemic exposure during gestation (DuPont 45278)are submitted as confidential data.

ECHA note - The following attachments were submitted with the comment above:
DuPont Confidential Reports (7).zip
Public Consultation of Thifensulfuron-methyl.pdf

Dossier Submitter's Response

Thank you for your comments and for the provision of new information. A summary of the new data will be included in the DS response to some of the comments received, where appropriate.

RAC's response

Noted. A discussion on the toxicity to reproduction data is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	Belgium		Individual	24

Comment received

FMC Chemical sprl(Cheminova AS)fully supports "no classification" for reproductive toxicity.
The CLH report clearly describes renal papillary findings in the original study as being within the normal continuum of renal development in the rat.
As new data to support "no classification", a new developmental toxicity study in rats was performed which was specifically targeted to examine the renal papilla (source of uncertainty in the first study as described in the CLH report). In the new GLP-compliant study, animals were dosed from gestation day (GD) 6 until GD 20 (in compliance with modern guidelines) and kidney and renal papilla of foetuses were examined at GD 21 (instead of GD 20, as in the preceding study).
No abnormalities of the kidney or renal pelvis were found.
In addition, an estimation of systemic exposure comparing the original developmental toxicity study and the multigeneration study, both estimated at GD19, is provided. The significance of GD19 is that this is approximately the start of development of the renal papilla in rats. In the developmental toxicity study, since dosing ceased at GD15,the systemic blood concentration of thifensulfuron methyl in pregnant dams would have

decreased to about 0.48 µg/mL by GD19. In contrast, in the multigeneration study with continuous dietary exposure, the systemic blood concentration at GD19 (and subsequently) would have been maintained at approximately 10-fold higher (4.4 µg/mL). If dose-related changes in the renal papilla were truly dose-related, they would therefore have been expected to be more evident in the multigeneration study than the previous developmental study. This is supported by the absence of histopathological changes in the kidneys from second generation weanlings in the muligeneration reproduction study. These new data support FMC Chemical sprl (Cheminova AS)position and the position of the CLH report that the distribution of renal pelvic findings in the original study is not abnormal, and represents a chance distribution of normal stages of renal development, for which no classification is appropriate. There is no evidence that the development of renal papilla was abnormal in any way.
The new developmental toxicity study and the study describing systemic exposure during gestation were already submitted by an other organisation as confidential data

Dossier Submitter's Response

Thank you for your comments. A summary of the new data will be included in the DS response to some of the comments received, where appropriate.

RAC's response

Noted. A discussion on the toxicity to reproduction data is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Sweden		MemberState	25

Comment received

The Swedish CA has some concerns regarding the available data and would like some clarifications to the arguments specified in the proposal to not classify Thifensulfuron-methyl (CAS 79277-27-3) as a reproductive toxicant. Furthermore, the way that the results of the studies are presented in the CLH-report makes it difficult for the reader to evaluate the studies thoroughly and to judge if the conclusion made by the DS is acceptable. A higher level of detail is indeed desirable.

Regarding the developmental toxicity study on rat (1984), we would like to have some clarifications on the following issues:

The historical control data
In this case, range alone is not a suitable measure when comparing the study results with historical control data. In our opinion, a statistical distribution with a mean and standard deviation would be preferred. OECD guidance document 43 states that "If historical control data are used, the most appropriate of these are from studies conducted in the same laboratory, within a reasonable amount of time prior to the study being interpreted (e.g., ± 2 years) in order to avoid genetic drift in the laboratory animal population, and under the same study conditions (e.g., identical species, strain, source, age, vehicle, route and duration of administration, technical personnel, etc.)."

Please compare the historical control data presented as a statistical distribution with a mean and standard deviation to the study results.

A wide range of historical control data over time may be the result of genetic variations over time influencing the control values. The time frame for the historical control data in

the present study is considered too wide according to OECD guidance document 43. Hence, more relevant historical control data in the time frame of ± 2 years in relation to the conduct of the study should be used in the assessment.

Please clarify if the study conditions for the historical control data are similar regarding rat strain, test facility etc.

Affected litters
We would like to know if the observed effects (small and absent renal papilla respectively, microphthalmia, skull bones partially ossified) are found in certain litters or if the observed effects are scattered in different litters. It could be of greater concern if the fetuses with malformations and growth variations are in different litters, rather than the same litter and this seems to be the case. The data in the CLH-report is presented as affected fetuses / litters. Some of the information on absent or small renal papilla can be found in the Renewal Assessment Report for Thifensulfuron-methyl. Although microscopic confirmation is lacking, absent renal papilla is a major malformation with cause for concern. When combining the data for absent and small renal papilla (assuming that absent renal papilla was in fact small renal papilla), effects are seen in 8 fetuses in 8 litters, at high dose. Therefore, we are reluctant to disregard this effect.

Maternal toxicity
Although the reduced maternal body weight gain was not statistically significant over the dosing period, a reduced body weight in a sensitive time frame for the fetus could possibly have an impact on fetal development. Please consider looking into individual data for the pregnant females and try to determine if effects on fetuses (small or absent renal papilla respectively, microphthalmia, partially ossified skull bones) are only observed in litters from females with significantly reduced body weight. We propose to perform a statistical analysis to determine if there is an association between maternal body weight and size of fetal renal papilla.

Fetal body weight and renal papilla development
We would like to know if there are any publications, more recent than 1970s, that show a correlation between reduced fetal body weight gain and the development of the kidney (renal papilla). We propose to perform a statistical analysis on the data in the rat developmental toxicity study (1984) to determine if there is an association between fetal body weight and size of renal papilla.

Microphthalmia
The incidence of microphthalmia was 2 fetuses in 2 litters at high dose (800 mg/kg bw/d) and 1 fetus in 1 litter at mid dose (200 mg/kg bw/d). This is a very rare malformation. Although the administered dose is high, the malformation is also observed at the lower dose of 200 mg/kg bw/d. We consider that this rare malformation should not be disregarded in the assessment of developmental toxicity, even if the result is not statistically significant. To clarify the importance/relevance of this effect, we would like to see a comparison of the incidence of microphthalmia with historical control data (that fulfil criteria of OECD guidance document 43), presented with a statistical distribution.

Dossier Submitter's Response

Thank you for your comments. In our opinion, the information relevant to the classification of thifensulfuron methyl has been included in the CLH report. Further details of studies can be found in the RAR, if required.

Historical control data:
Further information on the mean, standard deviation and distribution of the incidence of absent renal papilla in historical controls and on study conditions is provided with this RCOM table (as a confidential attachment). Of the 17 studies conducted by gavage as the rat thifensulfuron-methyl study during the period 1980-1989, a mean (± SD) of 0.8 (± 1.03) foetuses with absent renal papilla can be calculated. With regard to the distribution of the incidences of absent renal papilla, 9 studies have an incidence of 0 foetuses; 5 studies have an incidence of 1 foetus; 1 study has an incidence of 2 foetuses; and 2 studies have an incidence of 3 foetuses. Although OECD guidance document 43 states that relevant historical control data should be collected from studies conducted in a time frame of ± 2 years from the performance of the study of interest, the CLP guidance states that historical control data generated within a period of up to around 5 years of the study of interest are acceptable (see page 304 of the CLP guidance.)

Affected litters:
Information on whether the observed effects were found in certain litters or were scattered in different litters is not available to us.

Maternal toxicity, foetal body weight and renal papilla development:
The required analysis has already been performed and presented in the RAR:

Maternal and foetal body weight for foetuses observed to have absent or small renal papilla

Group	Dam #	Dam bwg 7-9	Dam bwg 7-17	Dam bwg7-21	Foetus #	Fatal wt.	Pap absent	Pap reduced
0	**361971**	11.9	68.1	130.7	3	3.83	X	
30	**361893**	4.6	45.3	91	1	3.77	X	
200	**362039**	7.7	51.5	103.7	5	3.76		X
800	**361902**	13	58.1	122.8	9	3.90		X
800	**361910**	13.6	63	126.9	1	3.47	X	
800	**361943**	15.2	93.2	169.1	3	3.56	X	X
800	**361999**	12.6	67.3	112.6	7	3.99	X	
800	**362011**	5.6	57.1	115.2	7	3.73		X
800	**362074**	5.6	48.8	116.8	9	3.46	X	
800	**362101**	8.5	51.8	100.7	7	3.82	X	
800	**362115**	6.9	50.7	106	9	3.69		X

As it can be seen from the table, no clear conclusions can be drawn from this small number of individual values with regard to the body weight of foetuses with absent or small renal papilla. In some animals with absent renal papilla, the body weight appears to be relatively low (e.g. 3.46, 3.47 or 3.56 g), while in other animals with absent renal papilla, the foetal weight is higher (e.g. 3.82 or 3.99 g). However, it is noted that 50% of the dams in the 800 mg/kg bw/d group that had offspring with "small/absent" renal papilla also had low body weight gain during gestation Days 7-9 as compared to the control mean value.

Microphthalmia:
The incidence of microphthalmia was marginally (but not statistically significantly) increased at 200 (1 foetus/1 litter vs 0/0 in controls) and 800 mg/kg bw/d (2 foetuses/2 litters vs 0/0 in controls). However, laboratory historical control data for microphthalmia in this strain of rat (range of 0/0 – 2 foetuses/2 litters from 33 developmental toxicity

studies conducted between 1982 and 1989) indicate that these findings were not related to treatment with thifensulfuron-methyl. Further information on the mean, standard deviation and distribution of the incidence of microphthalmia in historical controls and on study conditions has been requested from DuPont and is provided with this RCOM table. Of the 17 studies conducted by gavage as the rat thifensulfuron-methyl study during the period 1980-1989, a mean (± SD) of 0.3 (± 0.7) foetuses with microphthalmia can be calculated. With regard to the distribution of the incidences of microphthalmia, 14 studies have an incidence of 0 foetuses; 1 study has an incidence of 1 foetus; and 2 studies have an incidence of 2 foetuses.

Notwithstanding these concerns, please note that new data recently submitted by DuPont indicate that the original proposal from the DS (no classification for developmental toxicity) was appropriate. In a new GLP-compliant rat developmental toxicity study, animals (22/group) were dosed from gestation day (GD) 6 until GD 20 (in compliance with modern guidelines) at 0 and 800 mg/kg bw/d (the dose level at which the findings of absent/small renal papilla were seen in the original study) and kidney and renal papilla of foetuses were examined at GD 21 (instead of GD 20, as in the preceding study). In addition, external examinations of the foetuses were performed. No abnormalities of the kidney or renal pelvis were found. There was no evidence of microphthalmia.

In addition, an estimation (using data from the available kinetic studies) of systemic blood exposure at GD19 (start of development of renal papilla in rats) comparing the original developmental toxicity study and the multigeneration study shows that in the developmental toxicity study, since dosing had ceased at GD15, the systemic blood concentration of thifensulfuron methyl at the top dose of 800 mg/kg bw/d in pregnant dams had decreased to about 0.48 µg/mL by GD19. In contrast, in the multigeneration study with continuous dietary exposure, the systemic blood concentration at GD19 (and subsequently) at the top dose of 244 mg/kg bw/d in females had been maintained at approximately 10-fold higher (4.4 µg/mL). There were no histopathological changes in the kidneys from second generation weanlings in the multigeneration reproduction study despite the higher systemic blood exposure.

These new data support the position of the CLH report that the distribution of renal pelvic findings in the original developmental study is not abnormal, and represents a chance distribution of normal stages of renal development, for which no classification is appropriate.

RAC's response

Noted. A discussion on the toxicity to reproduction data is done in the ODD

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	France	Rotam Agrochemical Europe Ltd.	Company-Manufacturer	26

Comment received

Rotam Agrochemical Europe supports the proposal for "no classification" for reproductive toxicity" as proposed in the CLH report for thifensulfuron-methyl (March 2016) prepared by the United Kingdom, the Rapporteur Member State. As new data to support "no classification"', the main notifier submits a new developmental toxicity study in rats, specifically targeted to examine the renal papilla (source of uncertainty in the first study as described in the CLH report). In the new GLP-compliant study, animals were dosed from gestation day (GD) 6 until GD 20 (in compliance with modern guidelines) and kidney

and renal papilla of foetuses were examined at GD 21 (instead of GD 20, as in the preceding study). No abnormalities of the kidney or renal pelvis were found. In addition, an estimation of systemic exposure comparing the original developmental toxicity study and the multigeneration study, both estimated at GD19, is provided (DuPont45278). The significance of GD19 is that this is approximately the start of development of the renal papilla in rats. In the developmental toxicity study, since dosing ceased at GD15,the systemic blood concentration of thifensulfuron methyl in pregnant dams would have decreased to about 0.48 µg/mL by GD19. In contrast, in the multigeneration study with continuous dietary exposure, the systemic blood concentration at GD19 (and subsequently) would have been maintained at approximately 10-fold higher (4.4 µg/mL). If dose-related changes in the renal papilla were truly dose-related, they would therefore have been expected to be more evident in the multigeneration study than the previous developmental study. This is supported by the absence of histopathological changes in the kidneys from second generation weanlings in the multigeneration reproduction study. These new data support the position of the CLH report that the distribution of renal pelvic findings in the original study is not abnormal, and represents a chance distribution of normal stages of renal development, for which no classification is appropriate. There is no evidence that the development of renal papilla was abnormal in any way.
Dossier Submitter's Response
Thank you for your comments. A summary of the new data will be included in the DS response to some of the comments received, where appropriate.
RAC's response
Noted. A discussion on the toxicity to reproduction data is done in the ODD

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	Belgium		Individual	27
Comment received				
/				
Dossier Submitter's Response				
RAC's response				
n.a.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Netherlands		MemberState	28
Comment received				
The Dutch CA supports the proposed environmental classification of thifensulfuron-methyl as Aquatic Acute 1 (H400) with M-factor = 100 and Aquatic Chronic 1 (410) with M-factor 100.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2016	Belgium		MemberState	29
Comment received				
BE CA supports the proposed M-factors (Macute/Mchronic =100) for Thifensulfuron-methyl.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.04.2016	France		Individual	30
Comment received				
We agree with the classification and M factors proposed for Environmental hazards.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	Belgium		Individual	31
Comment received				
FMC Chemical sprl (Cheminova AS) fully supports the hazard aquatic classification proposed with the associated reliable studies.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	Finland		MemberState	32
Comment received				
We support the proposed classification for environmental hazards Aquatic Acute 1 with an acute M-factor of 100 and Aquatic Chronic 1 with a chronic M-factor of 100 for thifensulfuron-methyl.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2016	Germany		MemberState	33
Comment received				
The German CA supports the proposed environmental classification as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) as well as the acute and chronic M-factors of 100.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

NON-CONFIDENTIAL ATTACHMENTS

1. *Public Consultation of Thifensulfuron-methyl.pdf*. Submitted on 07/04/2016 by DuPont Crop Protection. [Please refer to comments No 6, 8, 14, 23]

CONFIDENTIAL ATTACHMENTS

1. *DuPont Confidential Reports (7).zip*. Submitted on 07/04/2016 by DuPont Crop Protection. [Please refer to comments No 6, 14, 23]
2. *DuPont-44802 -Thifensulfuron methyl technical developmental reproductibility toxicity in rats.zip.* Submitted on 07/04/2016 by DuPont Crop Protection. [Please refer to comments No 5]
3. *DE-MSCA Comments CLH-Thifensulfuron-methyl - Confidental.* Submitted on 19/04/2016 by German MSCA. [Please refer to comments No 1]