Committee for Risk Assessment

RAC

Annex 3
Records
of the targeted public consultation on the hazard classes STOT RE and reproductive toxicity of

MCPA-thioethyl (ISO); S-ethyl (4-chloro-2-methylphenoxy)ethanethioate; S-ethyl 4-chloro-o-tolyloxythioacetate

EC Number: 246-831-4
CAS Number: 25319-90-8

CLH-O-0000001412-86-194/F

Adopted

9 March 2018

ANNEX 3 - RECORDS OF THE TARGETED PUBLIC CONSULTATION ON THE HAZARD CLASSES STOT RE AND REPRODUCTIVE TOXICITY OF MCPA-THIOETHYL (ISO); S-ETHYL (4-CHLORO-2-METHYLPHENOXY)ETHANETHIOATE; S-ETHYL 4-CHLORO-O-TOLYLOXYTHIOACETATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

The proposal for the harmonised classification and labelling (CLH) of MCPA-thioethyl (ISO); S-ethyl (4-chloro-2-methylphenoxy)ethanethioate; S-ethyl 4-chloro-o-tolyloxythioacetate was submitted by the Polish competent authority and was subject to a public consultation from 21 February until 7 April 2017. The comments received by that date are compiled in Annex 2 to the opinion.

During its December 2017 meeting (RAC-43), the Committee for Risk Assessment (RAC) asked for further information to clarify the potential for MCPA-thioethyl to cause toxicity relevant for the hazard class specific target organ toxicity - repeated exposure (STOT RE). After RAC-43, the ECHA Secretariat received from the applicant three repeated dose toxicity studies (Hellwig et al., 1995, conducted with MCPA-DMA salt; Sadlonova et al., 2006 conducted with MCPA; Muckova et al., 2005 conducted with MCPA) that were not included in the original CLH proposal. The complete Reuzel et al., 1980 study conducted with MCPA, which was initially included in the CLH report, is also provided in this targeted PC for commenting.

During RAC-43, RAC did not discuss toxicity to reproduction as a research study (Roll and Matthiaschk, 1983 conducted with MCPA; in German) originally referred in the CLH dossier (but declared as being unavailable to the applicant) was made available to the Committee at a late stage of the process. This study was also within the scope of this targeted public consultation (launched on 17 with deadline for responses on 31 January 2017), available in both its original version and as an English translation.

Two additional research studies published (Ujházy et al., 2006; Yasuda M. and Maeda H., 1972) may also contain relevant information for reproductive toxicity classification. ECHA Secretariat provided the abstracts of these research studies.

COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during targeted public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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

Last data extracted on 01.02.2018

Substance name: MCPA-thioethyl (ISO); S-ethyl (4-chloro-2-methylphenoxy)ethanethioate; S-ethyl 4-chloro-o-tolyloxythioacetate
CAS number: 25319-90-8
EC number: 246-831-4
Dossier submitter: Poland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	Poland	National Institute of Public Health - National Institute of Hygiene	Academic institution	1
Comment received				
National Institute of Public Health - National Institute of Hygiene was involved as an expert institution in Poland acting as RMS for MCPA-acid, MCPA-thioethyl and MCPA-EHE. We feel				

obliged to maintain our position expressed in the Draft Renewal Assessment Report prepared for MCPA-acid, MCPA-thioethyl and MCPA-EHE in Volume 3 CA B.6 (AS) Toxicology and metabolism, and disagree with some proposals given in the consultation document: "The proposal for the harmonised classification and labelling (CLH) of MCPA-thioethyl (CAS 25319-90-8), submitted by Poland, was subject to a public consultation which ended on 7 April 2017". Based on the arguments given in the attached document we do not see the substantive grounds for the classification of MCPA-thioethyl as: 'toxic for reproduction' and 'specific target organ toxicity – repeated exposure'

ECHA note – An attachment was submitted with the comment above. Refer to public attachment MCPA-thioethyl_ECHA_public consulatation.pdf

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2018	Poland		MemberState	2
Comment received				
Bureau for Chemical Substances as CLH Submitter Dossier for MCPA is appreciate for the possibility of additional public consultations and the opportunity to send comments on this substance. During the preparation of the CLH dossier we concerned on studies previous accessible to us only. Currently we have possibility to analyze more detailly new data from study results provided in the discussion, which were not available to us beforehand. We have analyzed the research and would like to include our comments. We are still not sure if the tests results are sufficient for the classification for reproductive toxicity (adverse effects on sexual function and fertility, for adverse effects on development of the offspring) and for specific target organ toxicity after repeated exposure. These issues require further considerations.				

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	Spain	Sipcam Inagra, S.A.	Company-Manufacturer	3
Comment received				
The original application by the RMS for a harmonized classification is for MCPA Thioethyl. All the documentation (the CHL report, the ODD and the request for public comments) reflect this specific objective. In the RAR and in correspondence during the AIR administration, the RMS is not re-considering the existing harmonized classification for MCPA. Sipcam Inagra, S.A., as manufacturer of MCPA-thioethyl is surprised that MCPA acid data referenced in the CHL proposal is being unexpectedly considered to propose a toxicological classification for MCPA-thioethyl which differs from the established MCPA Harmonised Classification. The manufacturers of MCPA in the EU, as represented by the MCPA EU renewal Task Force have not had a timely opportunity to comment on the dossier. The submitted CLH dossier clearly identifies that exposure to the intact thioethyl ester is transient or topical and that longer-term or systemic exposure, particularly to mammals, is to the proximate metabolite, MCPA. The CLH proposal does not differentiate the classification between the acute effects attributable to the intact ester and the longer term, systemic effects that are only be attributable to the acid metabolite. Since it appears that the remit of the current classification exercise is to propose a harmonized classification for the thioethyl ester of MCPA, it might be an option to restrict the current evaluation to the direct (acute) effects of the ester and to refer to the existing				

harmonized classification for MCPA where the exposure exceeds an acute nature or where it is systemic.

In proposing Classification for repeat exposure organ toxicity (STOT RE) and for reproductive effects, the remit of the evaluation seems to have changed from an assessment of the intact ester to an assessment of MCPA acid.
In the AIR process, the evaluation of MCPA thioethyl relies on specific thioethyl ester data, but also in some cases on MCPA acid data where specific studies on the thioethyl are not available. Only these data appear to have been made available to the RAC committee. As a consequence the MCPA EU TF considers that the RAC committee has not evaluated the full data set for MCPA. (either as entire reports or summaries only).
Overall Sipcam Inagra, S.A., as manufacturer of MCPA-thioethyl agrees with this position.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final_Redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final.pdf

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	United Kingdom	MCPA EU Renewal Task Force	Company-Manufacturer	4

Comment received

The original application by the RMS for a harmonized classification is for MCPA Thioethyl. All the documentation (the CHL report, the ODD and the request for public comments) reflect this specific objective.
In the RAR and in correspondence during the AIR administration, the RMS is not re-considering the existing harmonized classification for MCPA. The MCPA TF is surprised and disappointed that MCPA acid data is being considered as part of the MCPA Thioethyl classification process.
Consequently, the manufacturers of MCPA in the EU, as represented by the MCPA EU renewal Task Force have not had a timely opportunity to comment on the dossier. The submitted CLH dossier clearly identifies that exposure to the intact thioethyl ester is transient or topical and that longer-term or systemic exposure, particularly to mammals, is to the proximate metabolite, MCPA. The CLH proposal does not differentiate the classification between the acute effects attributable to the intact ester and the longer term, systemic effects that are only be attributable to the acid metabolite.

Since it appears that the remit of the current classification exercise is to propose a harmonized classification for the thioethyl ester of MCPA, it might be an option to restrict the current evaluation to the direct (acute) effects of the ester and to refer to the existing harmonized classification for MCPA where the exposure exceeds an acute nature or where it is systemic.

In proposing Classification for repeat exposure organ toxicity (STOT RE) and for reproductive effects, the remit of the evaluation seems to have changed from an assessment of the intact ester to an assessment of MCPA acid.
In the AIR process, the evaluation of MCPA thioethyl relies on specific thioethyl ester data, but also in some cases on MCPA acid data where specific studies on the thioethyl are not

available. Only these data appear to have been made available to the RAC committee. As a consequence the MCPA EU TF considers that the RAC committee has not evaluated the full data set for MCPA. (either as entire reports or summaries only)

ECHA note – An attachment was submitted with the comment above. Refer to public attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final_Redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final.pdf

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	Poland	National Institute of Public Health - National Institute of Hygiene	Academic institution	5
Comment received				
See attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment MCPA-thioethyl_ECHA_public consulatation.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2018	France		MemberState	6
Comment received				
Developmental toxicity studies: In rat GLP studies reported in the CLH report (Tauchi, 1984- MCPA-thioethyl and Hellwig &Hildebrand, 1993 MCPA acid): - Decreased fetal weight and delayed ossification in presence of maternal toxicity. - No teratogenicity Yasuda M, 1972 (published) GLP: No (before GLP implementation) Guideline: not stated Oral in diet (gestation days 8-15) Test compound: MCPEE 0, 40 , 500, 1000 and 2000 ppm (about 0, 2.7, 30, 60 and 100 mg/kg bw/day, respectively) Purity: 94% Limitation: low and mid dose groups: less than 16 pregnant animals Results Dams: decreased BWG from 1000 ppm (60 mg/kg bw/day). Foetuses: decreased body weight and teratogenicity (increased incidence of cleft palate, ventricular septal defect and kidney malformations) from 1000 ppm (60 mg/kg bw/day) Increased post implantation loss at 2000 ppm (100 mg/kg bw/day). NOAEL mat and dev = 500 ppm (30 mg/kg bw/day) The author suggested that impurity profile of the tested compound should be performed				

especially the presence of TCDD (known strong embryotoxic compound).

In mouse
Roll and Matthiaschk, 1983 (published)
GLP: Not stated
Guideline: not stated
Oral gavage (gestation days 6-15)
Test compound: 0, 50, 100, 200, 300, 400 and 500 mg/kg bw/day
Limitation: purity: not reported, high dose group: less than 16 pregnant animals
Results
Dams: decreased BWG (body weight gain) from 300 mg/kg bw/day. MTD (maximal tolerable dose) reached at 500 mg/kg bw/day
Foetuses: decreased body weight from 100 mg/kg bw/day. Postimplantation loss from 300 mg/kg bw/day.
Teratogenicity: increased malformation from 200 mg/kg bw/day (increased incidence cleft palate, wavy ribs).
The author suggested that teratogenic effects observed in rodents may result from an inhibition of the embryotrophic nutrition via the inverted yolk sac (InYS).

In rabbit
Studies reported in the CLH report (Sakamaki, 1985 MCPA-thioethyl; Hellwig &Hildebrand, 1993 and Irvine, 1980 MCPA acid)
- No teratogenicity, no effect on fetal body weight.

Ujházy et al, 2006 (published)
GLP: Yes
Guideline: not stated # OECD 414
Oral gavage (gestation days 6-27)
Test compound: 0, 5, 10 and 25 mg/kg bw/day
Purity: MCPA, CAS94-76-4, Karanth, 2005) (Sample No. 176, Certificate No. 1056)
Limitation: high dose group: less than 16 pregnant animals. No maternal toxicity observed at any dose level.
Dams: No effect on BWG
Decreased placental weight at 25 mg/kg bw/day.
Foetuses: decreased fetal body weight at 25 mg/kg bw/day and delayed ossification from 5 mg/kg bw/day. No teratogenic effect.

☐ Comparison with criteria for classification
- Death of the developing organism: Postimplantation loss reported in presence of maternal toxicity in rat and mouse (published studies: Yasuda M, 1972; Roll and Matthiaschk, 1983; Ujházy et al, 2006) but not observed in unpublished studies reported the CLH report.
- Structural abnormality: Not teratogenic in rabbit or rat studies reported in the CLH dossier. In published studies, the substance is teratogenic in rat at materno-toxic doses and in mouse from dose level with no concurrent maternal toxicity.
- Altered growth: in rat, decreased fetal weight and delayed ossification were observed in presence of maternal toxicity. In mouse, decreased fetal weight was observed from dose level with no concurrent maternal toxicity. In rabbit, decreased fetal weight and delayed in the absence of maternal toxicity (Ujházy et al, 2006).

As regard teratogenic effects observed in rodents in published studies, they may be secondary to inhibition of embryotrophic nutrition via the inverted yolk sac as mentioned by Roll and Matthiaschk (1983) which could explain that such effects were not observed in

rabbit (inYS). Indeed, while an inverted yolk sac also exists in rabbit at the same period, there are important anatomic differences: inYS is not in direct contact with uterus and it does not totally enclose the embryo, playing therefore a limited role in dam/foetus exchanges. In that respect, the rabbit might be a more predictive model for human (absence of inverted yolk sac in human placentation)1. For instance, glycolic acid (GA) was shown to be teratogenic in rodents (skeletal and craniofacial malformations) but not in rabbit. The lower exposure of the rabbit embryo was related to the negligible role of its inYS compared to that in rat along with the large volume of slightly acidic extra-embryonic fluid, features shared by human embryos at the same stage (absence of inYS and large volume of slight acidic celomic fluid) 2.
On the other hand, the discrepancies between rodents and rabbit may also come from the higher doses tested in rodents. Among rodent studies, the discrepancies between published studies and studies reported in the CLH report may result from different impurities profile of the batches tested (Yasuda M, 1972).

As regard altered growth, it is noteworthy that such effects (decreased foetal weight and delayed ossification) were observed the absence of maternal toxicity in a published GLP study in rabbit (Ujházy et al, 2006) as well as in mouse in Roll and Matthiaschk, 1983, suggesting higher sensitivity of developing organisms.

Based on those data, a classification for development toxicity is considered warranted.

Considering the absence of teratogenic effects in rabbit studies and in GLP rodent studies, the uncertainties linked to the unknown purity of the tested compounds in the published studies, the fact that rodent may not be the most appropriate model for this kind of compounds, a category 2 is considered appropriate based on foetal altered growth observed in the absence of maternal toxicity.

1 Carney EW, Scialli AR, Watson RE, DeSesso JM. Mechanisms regulating toxicant disposition to the embryo during early pregnancy: an interspecies comparison. Birth Defects Res (C): Embryol Today 2004;72:345–60.

2 Carney EW, Tornesi B, Markham DA, Species-Specificity of Ethylene Glycol-induced Developmental Toxicity: Toxicokinetic and Whole Embryo Culture Studies in the Rabbit. Birth Defects Res B Dev Reprod Toxicol. 2008 Dec;83(6):573-81

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2018	Poland		MemberState	7

Comment received

In the prepared CLH dossier available studies concerning reproductive toxicity were evaluated, which, in our opinion, do not trigger classification both for adverse effects on sexual function and fertility as for adverse effects on development of the offspring.

Fertility
Based on previous studies on fertility the included in the CLH application dossier submitter did not classified the substance in active toxicity for reproduction.
Currently two studies placed for consultation do not concern reproductive effects, however, they show the effects on development on spermiogenesis in beagle dogs (I. Sadlonova et al., 2006; M. Muckova et all., 2005). However, the result obtained in the first study indicate that changes were reversible. In the second one there is information on adverse effect on

development of spermiogenesis. Testicular atrophy and occurrence of the multinucleate giant cells were observed in one animal and absence of spermatogenic cells in several tubules was observed in other one. Both animals were from the highest dose group. In our opinion the fact that two other animals were affected with other symptoms should be regarded as not enough for classification as reproductive substance. Small focal absence of spermatogenic cells in tubules of testis were not take into consideration for classification purpose.
Taking into account all available studies we are of the opinion that result could be not sufficient for triggering of classification for reproductive toxicity.

Developmental toxicity
The developmental toxicity presented in previous studies on rat and rabbit was evaluated in CLH dossier. A study of the developmental toxicity of MCPA in the mouse published by R. Roll and G. Mattiaschk (1983) was also concerned in CLH dossier although the original report and data were not available to the applicant for assessment and the quality of the study was unknown. Neither the source nor purity of the test material used in this study is reported.
Malformation occurred with MCPA from 200 mg/kg were in the form of cleft palates and wavy ribs. We would like to underline that NMRI mice strain, used in presented test, has a high background incidence of cleft palate. This fact can indicates that the study should not be regarded as appropriate for classification as reproductive toxicity (developmental).

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	Spain	Sipcam Inagra, S.A.	Company-Manufacturer	8

Comment received

The reproductive hazard classification is discussed by the RAC in the revised ODD. There are a number of studies available for assessment carried out using 3 indicator species, however by and large the decision appears to be influenced by effects seen in an early (1983) study in the mouse by Roll and Mattiaschk. The MCPA EU renewal Task Force points out that this study has been reviewed previously for the original Annex I inclusion (which included a PEER review process) and more recently for the renewal (AIR) process. On these occasions the weight of evidence from the study was considered insufficient to outweigh that of more recent and guideline teratology studies. The MCPA EU renewal Task Force has prepared a review of the teratology data and in particular a critique of this study. It concludes that the study is unreliable and should not be used to drive a classification decision. This opinion is provided in the attached document "EU MCPA Taskforce response to CLH reproduction classification proposal for MCPA thioethyl ester"
Sipcam Inagra, S.A., as manufacturer of MCPA-thioethyl agrees with this position.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final_Redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final.pdf

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	United Kingdom	MCPA EU Renewal Task Force	Company-Manufacturer	9
Comment received				
The reproductive hazard classification is discussed by the RAC in the revised ODD. There are a number of studies available for assessment carried out using 3 indicator species, however by and large the decision appears to be influenced by effects seen in an early (1983) study in the mouse by Roll and Mattiaschk. The MCPA EU renewal Task Force points out that this study has been reviewed previously for the original Annex I inclusion (which included a PEER review process) and more recently for the renewal (AIR) process. On these occasions the weight of evidence from the study was considered insufficient to outweigh that of more recent and guideline teratology studies. The MCPA EU renewal Task Force has prepared a review of the teratology data and in particular a critique of this study. It concludes that the study is unreliable and should not be used to drive a classification decision. This opinion is provided in the attached document "EU MCPA Taskforce response to CLH reproduction classification proposal for MCPA thioethyl ester" ECHA note – An attachment was submitted with the comment above. Refer to public attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final_Redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final.pdf				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	Poland	National Institute of Public Health - National Institute of Hygiene	Academic institution	10
Comment received				
See attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment MCPA-thioethyl_ECHA_public consulatation.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2018	France		MemberState	11
Comment received				
Repeated dose toxicity studies in dogs: Hellwig et al., 1995 GLP: yes Guideline: OECD409 No deviation Acceptable Test compound: MCPA-DMA Salt (purity 99.9% eq to 63.4% MCPA acid)				

Dietary study 0, 20, 80 and 360 ppm (eq to 0, 0.6/0.7, 2.4/2.9 and 10.9/12.8 mg/kg bw/day in M/F)
Beagle dogs (4/sex/dose)
No mortality, no effect on BW or BWG
At 0.6/0.7 mg/kg bw/day:
no adverse effect
At 2.4/2.9 mg/kg bw/day:
Kidney: increased creatinine in both sexes, increased urea in females
At 10.9/12.8 mg/kg bw/day:
Kidney: increased creatinine and urea in both sexes
Liver: increased ALT in both sexes, decreased thromboplastin time in females and subacute to chronic interstitial hepatitis in ¼ males and ¾ females.

It is noteworthy in the study report a 1-year dog performed with MCPA acid is mentioned. This study is not reported in the CLH dossier but was assessed by US-EPA and California EPA (http://www.cdpr.ca.gov/docs/risk/toxsums/pdfs/786.pdf)

Hellwig (1986) (unpublished)
According to text in the study report:
MCPA (purity = 94.8%)
Beagle dogs (6/sex/dose) at 0, 6, 30, or 150 ppm for 12 months (eq to 0, 0.2, 1 & 5 mg/kg/day)
At 0.2 mg/kg bw/day:
No adverse effect
At 1 mg/kg bw/day:
Decreased BWG males, decreased food consumption females
Kidney: increased creatinine in both sexes and K+ in females; dark brown coloration of kidney increased pigment storage (lipofushin) in epithelia of the proximal portion of the renal tubules in 4/6 females
At 5 mg/kg bw/day:
Decreased BWG males, decreased food consumption females
Kidney: increased creatinine and urea in both sexes and K+ in females; dark brown coloration of kidney increased pigment storage (lipofushin) in epithelia of the proximal portion of the renal tubules in 4/6 males and 6/6 females.

In Sadlonova et al., 2006 conducted with MCPA and Muckova et al., 2005 conducted with MCPA) the same study is reported.
GLP: yes
Guideline: OECD409
No deviation
Acceptable
Test compound: MCPA (97%)
Capsule 0, 1, 5 and 15mg/kg bw/day + satellite group
Beagle dogs (4/sex/dose)
No mortality, no effect on BW or BWG
At 1 mg/kg bw/day:
Kidney: increased creatinine in both sexes
At 5 mg/kg bw/day:
Kidney: increased creatinine and urea in both sexes
Liver: increased ALT in both sexes
At 15 mg/kg bw/day:
Decreased glucose

Kidney: increased creatinine and urea in both sexes
Liver: increased ALT in both sexes, focal hepatocellular necrosis
Testes: decreased relative weight, focal atrophy, multinucleate giant cell (1/4 male) and absence of spermatogenesis (1/4 male)
Biochemical changes were reversible.

Reuzel, 1980
GLP: before GLP implementation
Guideline: not stated # OECD 409
Deviation High dose clearly exceeding the MTD
Acceptable
Test compound: MCPA-DMA Salt (purity 99.9% eq to 63.4% MCPA acid)
Feeding study diet to provide intakes of 0, 0.3, 1, 3, 12 and 48 mg/kg bw/day
Beagle dogs (4/sex/dose)
Up to 1 mg/kg bw/day:
No effect
At 3 mg/kg bw/day:
Kidney: increased creatinine and urea in both sexes
Liver: increased GPT in both sexes
At 12 mg/kg bw/day:
Decreased BWG, faecal blood
Kidney: increased creatinine and urea in both sexes
Liver: increased ALT and GPT in both sexes, infiltrates of mononuclear cells, bile duct proliferation
At 48 mg/kg bw/day:
Mortality, weight loss, clinical signs (diarrhoea, faecal blood, lethargy, anorexia, stomatitis, necrotic skin…)
Decreased glucose
Kidney: increased creatinine and urea, increased relative weight, degenerative/regenerative lesions
Liver: increased ALT GPT and bilirubin, decreased albumin and total protein degenerative/regenerative lesions, icterus, enlarge gall bladder

Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE:

Kidney and liver were the target organs in the all the 90-day studies in dog.
Biochemical parameters of kidney and liver were consistently impacted from 2/3 mg/kg bw/day onwards. As regard severity, liver histopathological findings were observed: chronic interstitial hepatitis at 10.9/12.8 mg/kg bw/day (Hellwig, 1995), focal necrosis at 15 mg/kg bw/day (Muckova, 2005) and liver inflammation at 12 and necrosis at 48 mg/kg bw/day respectively (Reuzel, 1980).
Renal degenerative/regenerative lesions were also observed in top dose animals (Reuzel, 1980). Furthermore, it cannot be excluded that the severe clinical symptoms observed in 7/8 high dose dogs were consecutive of renal failure.
In Hellwig, 1995 it is also reported that kidney increased pigment storage (lipofushin) in epithelia of the proximal portion of the renal tubules was observed from 1 mg/kg bw/day in a 1-year dog study.

Based on the above mentioned considerations, France is of the opinion that classification as STOT RE category 2 (liver and kidney) is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2018	Poland		MemberState	12
Comment received				

In our opinion, taking into account studies which were presented in our CLH dossier for MCPA-thioethyl, no classification for STOT RE for mentioned substance is required.
However, in the light of recently uploaded studies we have doubts regarding specific target organ toxicity profile of MCPA-thioethyl.
There are two relatively new studies performed in compliance with the principles of GLP and with the adoption of accepted regulatory guidelines - Sadlonova et al., 2006 and Muckova et al., 2005, both conducted with MCPA.
Firstly, we would like to emphasize that in a dog 90-day oral study (Muckova et al., 2005) there are lack of relevant information regarding reversibility of the changes. Both dog 90-day oral studies (Sadlonova et al., 2006 and Muckova et al., 2005) have shown changes of biochemical parameters such as increase of ALT, urea, creatinine, decrease of ALP and clinical changes, such as inflammatory lesions in the liver and moderate damage of the kidney. In the study of Sadlonova et al., 2006 all changes were reversible. Whereas, in the Muckova et al., 2005 study "reversible changes" seem to be related only to biochemical parameters what is misleading in terms of interpretation whether the classification criteria have been met.
However, we would like to underline that even though liver lesions are irreversibly, the main relevant change was focal hepatocellular necrosis (observed merely in animals treated with the highest dose of 15 mg/kg MCPA), whereas only multi-focal or diffuse necrosis is listed as one of the effects supporting classification for STOT RE in CLP Regulation.
Quite different results were obtained during dog 110-118 days study (Hellwig et al., 1995). One of the histopathological findings was subacute to chronic interstitial hepatitis in one male and three out of four female dogs accompanied by increase of alanine aminotransferase. In discussion and conclusions of mentioned studies this lesion is considered as persistent hepatotoxic effect. This finding was observed in the highest tested oral dose corresponding to 11.8 mg/kg body weight/day what could trigger category 2 of STOT RE. However, we would like to also stressed that this study is none GLP.
Regarding 90 day dog study which was already considered in our CLH dossier (Reuzel et al., 1980) we can see that dose level of 48 mg/kg bw/day has caused severity of clinical findings. However, in the light of the age of this study (none GLP and without adoption of any accepted regulatory protocols) these results should be treated with caution. Therefore, priority should be given to the results from the Sadlonova et al., 2006 and Muckova et al., 2005, performed in compliance with the principles of GLP and with the adoption of accepted regulatory guidelines.
Finally, we would like to underline that in the open literature (e.g. Timchalk, 2004) there are evidences that dogs are particular susceptible species for this class of herbicides and we have doubts if dogs are adequate experimental animal species for classification purposes of MCPA-thioethyl.
However, without a doubt specific target organ toxicity following repeated exposures to a MCPA-thioethyl needs to be deeply considered in the light of recently received data, especially with the liver as the target organ.

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	Spain	Sipcam Inagra, S.A.	Company-Manufacturer	13

Comment received

RAC consider that MCPA-thioethyl reach the requirement for classification for STOT RE based on the effects in the gastro-intestinal tract, in the liver and for lethality all effects attributed to the 90 days dog study by Reuzel et al. 1980 in the highest dose 48 mg/kg bw/d.

It is the opinion of the MCPA EU Renewal Task Force that the effects seen in the top dose of this study cannot reliably be attributed to a systemic exposure to MCPA. The gross pathology clearly shows that there was hemorrhage to the buccal cavity, stomach and intestines and the presence of faecal blood. This is most likely due to the topical effect of the acid MCPA on the mucous membranes and gut lining (weak organic acids are known to be cause ulceration eg aspirin). The animals on this highest dose of MCPA clearly had prolonged intestinal ulceration and blood loss, and this would have masked any true systemic effects. (oesophageal and stomach ulceration have been seen in other phenoxy acid toxicological studies, particularly where the dose is administered by gavage. (It is acknowledged that in this case the dog was given MCPA in the diet, but we know that the dog is particularly sensitive to weak organic acids).
The dose of 48 mg/kg/day clearly exceeded the MTD, 7/8 of the dogs showed severe clinical signs, one dog died (day 48) and six others were sacrificed in-extremis up to day 63.

A STOT RE classification is designed to give credible and realistic health advice for humans. There are three reasons why the TF believes that the use of this data cannot be considered as giving reliable information useful for prediction of human hazard.
1) The RAC committee considers that lethality seen at 48 mg/kg/day is sufficient for a STOT RE classification. However, the effects seen at this dose are heavily influenced by the topical effects caused on the GI tract. The TF believes that the high degree of damage to the buccal cavity, stomach and intestine is caused by the acidic nature of the MCPA. The subsequent loss of integrity of the GI mucosae will have facilitated rapid uptake of the MCPA and many of the clinical signs seen would be secondary toxicity caused by blood loss. In this study the maximum tolerated dose (MTD) was clearly exceeded at the high dose and concluding any specific effects as attributable directly to MCPA is impossible. Repeated exposure in this manner to humans is not tenable and therefore has no relevance to the protection of humans. It is only a manifestation of the particular toxicological protocol. The fact that the animals had to be sacrificed early on humane grounds is indicative of the fact that the MTD was exceeded and that the study was poorly conceived and yields little useful data on which to predict repeat dose organ specific toxicity.

2) The effects seen in the dog are not evident in other model species tested (even at much higher doses). The RAC committee has examined the evidence to demonstrate that the dog is a peculiarly sensitive species to the effects of phenoxy acids and is atypical of humans. This sensitivity will have been exacerbated by the rapid intake of test material as the integrity of the GI tract membrane was compromised.

3) Finally, the RAC committee is using data derived from a study on MCPA acid to define a hazard classification for MCPA thioethyl ester. If it is accepted that the effects on the dog in the Reuzel study are at least in part influenced by a topical effect on the GI tract, then it may be unwise to read across from acid to ester. The relative irritancy of MCPA acid vs MCPA esters is of importance. Neither MCPA Thioethyl nor the other ester variant (MCPA

EHE) is proposed as an eye irritant. In contrast the effect of MCPA acid on the eye is severe and warrants classification as a severe irritant. This emphasizes that it is not possible to extrapolate the effects of MCPA acid where effects are from topical exposure.

Whilst the lethality, to the dog, of repeat dose exposure to MCPA cannot be denied, its relevance to human hazard is questionable as is its extrapolation to MCPA Thioethyl. Sipcam Inagra, S.A., as manufacturer of MCPA-thioethyl agrees with this position.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final_Redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final.pdf

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	United Kingdom	MCPA EU Renewal Task Force	Company-Manufacturer	14

Comment received

RAC consider that MCPA-thioethyl reach the requirement for classification for STOT RE based on the effects in the gastro-intestinal tract, in the liver and for lethality all effects attributed to the 90 days dog study by Reuzel et al. 1980 in the highest dose 48 mg/kg bw/d.

It is the opinion of the MCPA EU Renewal Task Force that the effects seen in the top dose of this study cannot reliably be attributed to a systemic exposure to MCPA. The gross pathology clearly shows that there was hemorrhage to the buccal cavity, stomach and intestines and the presence of faecal blood. This is most likely due to the topical effect of the acid MCPA on the mucous membranes and gut lining (weak organic acids are known to be cause ulceration eg aspirin). The animals on this highest dose of MCPA clearly had prolonged intestinal ulceration and blood loss, and this would have masked any true systemic effects. (oesophageal and stomach ulceration have been seen in other phenoxy acid toxicological studies, particularly where the dose is administered by gavage. (It is acknowledged that in this case the dog was given MCPA in the diet, but we know that the dog is particularly sensitive to weak organic acids).
The dose of 48 mg/kg/day clearly exceeded the MTD, 7/8 of the dogs showed severe clinical signs, one dog died (day 48) and six others were sacrificed in-extremis up to day 63.

A STOT RE classification is designed to give credible and realistic health advice for humans. There are three reasons why the TF believes that the use of this data cannot be considered as giving reliable information useful for prediction of human hazard.
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protection of humans. It is only a manifestation of the particular toxicological protocol. The fact that the animals had to be sacrificed early on humane grounds is indicative of the fact that the MTD was exceeded and that the study was poorly conceived and yields little useful data on which to predict repeat dose organ specific toxicity.

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PUBLIC ATTACHMENTS
1. MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final_Redacted.pdf [Please refer to comment No. 3, 4, 8, 9, 13, 14]
2. MCPA-thioethyl_ECHA_public consulatation.pdf [Please refer to comment No. 1, 5, 10]

CONFIDENTIAL ATTACHMENTS
1. MCPA EU Taskforce response to proposed classification on MCPA thioethyl ester_January 2018 Final.pdf [Please refer to comment No. 3, 4, 8, 9, 13, 14]