Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level 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

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9 March 2018

CLH-O-0000001412-86-194/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name:	**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**

The proposal was submitted by **Poland** and received by RAC on **2 November 2016.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Poland has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **21 February 2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **7 April 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC:	**Peter Hammer Sørensen**
Co-Rapporteur, appointed by RAC:	**Steve Dungey**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **9 March 2018** by **consensus**.

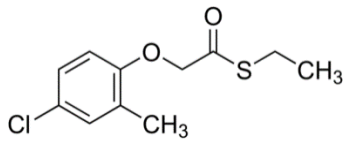
Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	607-RST-vW-Y	MCPA-thioethyl (ISO); S-ethyl (4-chloro-2-methylphenoxy)ethan ethioate; S-ethyl 4-chloro-o-tolyloxythioacetate	246-831-4	25319-90-8	Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1	H302 H400 H410	GHS07 GHS09 Wng	H302 H410		M=10 M=10	
RAC opinion	607-RST-vW-Y	MCPA-thioethyl (ISO); S-ethyl (4-chloro-2-methylphenoxy)ethan ethioate; S-ethyl 4-chloro-o-tolyloxythioacetate	246-831-4	25319-90-8	Acute Tox. 4 STOT RE. 2 Aquatic Acute 1 Aquatic Chronic 1	H302 H373 (liver) H400 H410	GHS07 GHS08 GHS09 Wng	H302 H373 (liver) H410		oral: ATE = 450 mg/kg bw M=10 M=10	
Resulting Annex VI entry if agreed by COM	607-RST-vW-Y	MCPA-thioethyl (ISO); S-ethyl (4-chloro-2-methylphenoxy)ethan ethioate; S-ethyl 4-chloro-o-tolyloxythioacetate	246-831-4	25319-90-8	Acute Tox. 4 STOT RE. 2 Aquatic Acute 1 Aquatic Chronic 1	H302 H373 (liver) H400 H410	GHS07 GHS08 GHS09 Wng	H302 H373 (liver) H410		oral: ATE = 450 mg/kg bw M=10 M=10	

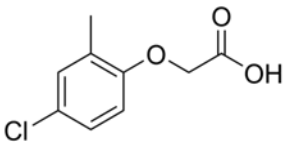
GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Read-across approach for using the data obtained from MCPA



MCPA-thioethyl
Formel: $C_{11}H_{13}ClO_2S$
Molecular Weight 244.74 g/mol



MCPA
Formel: $C_9H_9ClO_3$
Molecular weight: 200.62 g/mol

^{14}C-MCPA-Thioethyl was administered orally to Sprague-Dawley rats kept in metabolic cages at doses of 5 and 100 mg/kg. Urine, faeces and expired gases were separately collected and analysed. The radioactivity in most tissues peaked between 2 and 8 hours and decreased very rapidly, indicating that the active ingredient and its metabolites are completely eliminated. Most of the radioactivity was eliminated in the urine. The analysis of the metabolites indicated that the parent compound is rapidly degraded and that MCPA is quantitatively the major metabolite found.

The metabolism of ^{14}C-MCPA-Thioethyl was extensively studied in rats. The main outcome of this study was that the parent compound underwent a very rapid biotransformation to the acid metabolite MCPA since the parent compound was detected only in traces in the urines and faeces of the treated rats. This is a rather expected pathway since the breakdown of the ester bond was the first metabolic event. MCPA itself undergoes a further extensive biodegradation. These observations are significant since the overall toxicological pattern of MCPA should be taken into consideration in making the final hazard assessment for MCPA-Thioethyl (Ohyama H, 1977).

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

MCPA-thioethyl had a moderate acute oral toxicity to rats with an LD_{50} of 450 mg/kg bw in rats and 580 mg/kg bw in mice. Published human data available on MCPA gives the lowest human lethal dose as 814 mg/kg bw. MCPA-thioethyl was of low acute dermal toxicity to rats (LD_{50}> 5000 mg/kg bw) and the four-hour LC_{50} via inhalation of MCPA-thioethyl to rats was > 5 mg/L. Based on these data, the dossier submitter (DS) proposed classification as Acute Tox. 4, H302 with an ATE value of 450 mg/kg.

Comments received during public consultation

Two Member state competent authorities (MSCAs) agreed with the propsal.

Assessment and comparison with the classification criteria

RAC agrees that with a rat oral LD_{50} of 450 mg/kg bw, MCPA-thioethyl warrants classification as **Acute Tox. 4; H302 according to CLP, with an ATE value of 450 mg/kg**.

MCPA-thioethyl has low acute dermal and inhalation toxicity (LD_{50} >5000 mg/kg bw and LC_{50} >5 mg/L (dust), respectively) and therefore does not warrant classification via these routes under CLP.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

There were no indications of specific organ toxicity in the single exposure acute studies (Itoh and Toida, 1974; Dickhaus, 1991) including an acute neurotoxicity study (Mellert *et al*. 1994a).

No signs of systemic toxicity were evident after exposure to acute limit doses of MCPA-thioethyl in animal studies via the dermal or inhalation routes (Dickhaus, 1991a; Kobayashi, 1983; Church, 1984; Mulier, 2003).

In humans, 20 years of biyearly monitoring of plant workers revealed no significant adverse effects in workers and no reports of allergenicity. No cases of poisoning were reported on the production plant between 1971 and 2002.

Comments received during public consultation

No comments received.

Assessment and comparison with the classification criteria

There was no evidence for specific target organ toxicity following single exposures to MCPA-thioethyl via the oral, dermal or inhalation routes, and therefore **classification for STOT-SE is not warranted**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The skin irritation potential of MCPA-thioethyl has been investigated in a standard guideline study in rabbits, and in a non-GLP, non-guideline study. MCPA-thioethyl did not show any signs of skin irritation of rabbits.

Comments received during public consultation

No comments received.

Assessment and comparison with the classification criteria

RAC agrees that as no signs of erythmea or oedema were observed (also no inflammation persisting to the end of the observation period) was seen, **MCPA-thioethyl does not meet the criteria for classification of skin corrosion/irritation** according to the CLP Regulation.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

Table of relevant eye irritation studies:

<table>
<tr><th>Method</th><th>Results and Remarks</th><th>Reference</th></tr>
<tr><td>Rabbit (New Zealand White)
3 male and 3 female
Similar to OECD TG 405
GLP
Test Material: MCPA-thioethyl (Purity: IUCLID technical dossier)
0.1g into conjunctival sac
Observed for 7 days</td><td>Slight conjunctival redness with secretion for up to 8 hours after instillation of the test substance.
Sum of (conjunctival+chemosis+lacrimation) x2 scores
<table>
<tr><td></td><td>1M</td><td>2M</td><td>3M</td><td>4F</td><td>5F</td><td>6F</td></tr>
<tr><td>1h</td><td>4</td><td>4</td><td>4</td><td>4</td><td>4</td><td>4</td></tr>
<tr><td>2 h</td><td>4</td><td>4</td><td>4</td><td>4</td><td>4</td><td>4</td></tr>
<tr><td>4 h</td><td>6</td><td>6</td><td>4</td><td>6</td><td>6</td><td>4</td></tr>
<tr><td>8 h</td><td>4</td><td>4</td><td>2</td><td>4</td><td>4</td><td>2</td></tr>
<tr><td>24 h</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
</table>
Under the conditions of this study, MCPA-thioethyl is considered as non-irritant to rabbit eyes.</td><td>Dickhaus, 1991e</td></tr>
<tr><td>Rabbit (Japanese White)
3 male and 3 female
Guideline not stated – similar to OECD TG 405
Not GLP
Test Material: MCPA-thioethyl (Purity: IUCLID technical dossier)
0.1 g into conjunctival sac.
Observed for 7 days</td><td>Slight conjunctival redness in all animals at 24 h with slight discharge. All animals had recovered by day 4.
Sum of (conjunctival + chemosis + lacrimation) x2 scores
<table>
<tr><td></td><td>1M</td><td>2M</td><td>3M</td><td>1F</td><td>2F</td><td>3F</td></tr>
<tr><td>24 h</td><td>2</td><td>2</td><td>2</td><td>8</td><td>6</td><td>2</td></tr>
<tr><td>48 h</td><td>0</td><td>0</td><td>0</td><td>4</td><td>0</td><td>0</td></tr>
<tr><td>72 h</td><td>0</td><td>0</td><td>0</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>4 d</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
</table>
Under the conditions of this test, MCPA-thioethyl is slightly irritant to rabbit eyes, but the criteria for classification are not met.</td><td>Kobayashi, 1982</td></tr>
</table>

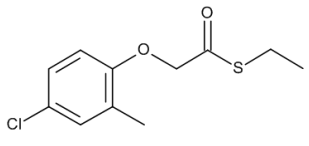
In the Dickhaus (1991e) study, all animals showed slight conjunctival redness and slight oedema for up to 8 h after exposure, but all animals showed recovery at the 24 h observation time point. In a previous non-GLP study (Kobayashi, 1982), slight conjunctival redness was observed in all animals at 24 hours with slight discharge. All animals except for one female had fully recovered by 48 hours, with the latter showing recovery by day 4.

Comments received during public consultation

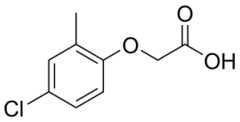
One MSCA commented that Table 13 "Summary table of relevant eye irritation studies" on page 30 was not fully comprehensible and did not facilitate a comparison with the CLP criteria. In both studies, 6 animals (males and females combined) were used but a comparison with the criteria were performed using criteria that are applicable for a study with three rabbits (CLP, Annex I, 4.4.2.4). For calculation of mean scores corneal, iris and conjunctival effects should be taken into account. The MSCA commented that a rather unusual approach was taken in Table 13 to present the data, and that according to the text, the DS's proposal of no classification might be appropriate but the arguments should be presented in a more convincing way. This is particularly important since MCPA was already classified as Eye Dam. 1 and for this closely related compound there are several studies available which have shown serious eye damage in rabbits.

Assessment and comparison with the classification criteria

Regarding the comparison of MCPA and MCPA-thioethyl: MCPA is the acid and MCPA-thioethyl is the thio-ester of MCPA. Therefore the irritatant properties may be different. MCPA is classified as Eye Dam.1.



MCPA-thioethyl



MCPA (Acid)

Although read across is in many cases valid, for Serious eye damage/eye irritation it may not be justified to read across from an acid to an ester.

There are 2 studies with MCPA-thioethyl. In both cases 6 rabbits were used instead of the 3 required in OECD TG 405. The Dickhaus study showed no findings in any animal after 24, 48 or 72 hours. Using the standard presentation the data is as follows:

	Mean score 24, 48 and 72 hours after instillation					
Ocular structure/finding	**1**	**2**	**3**	**4**	**5**	**6**
Cornea	0	0	0	0	0	0
Iris	0	0	0	0	0	0
Conjunctiva - redness	0	0	0	0	0	0
Conjunctiva - chemosis	0	0	0	0	0	0

In the Kobayashi study there are no findings in the iris or cornea of any animal. The individual data are summarised below:

	Mean score 24, 48 and 72 hours after instillation					
Ocular structure/finding	**1M**	**2M**	**3M**	**4F**	**5F**	**6F**
Cornea	0	0	0	0	0	0
Iris	0	0	0	0	0	0
Conjunctiva - redness	0.3	0.3	0.3	1.3	0.3	0.3
Conjunctiva - chemosis	0	0	0	0	0	0.3

None of the 6 animals tested presented a mean conjunctival score ≥ 2 for either redness or chemosis. All findings had fully reversed by 4 days after instillation of MCPA-thioethyl.

RAC agrees that the results of 2 independent studies with MCPA-thioethyl in a total of 12 rabbits **do not support classification for eye irritation**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Table with relevant studies:

Method	Results and Remarks	Reference
Guinea Pig (Hartley) Maximisation test (Magnusson and Kligman) Males: 23 animals were induced and challenged with MCPA-thioethyl; 10 were induced with paraffin oil and challenged with MCPA-thioethyl; a further 5+5 animals acted as controls. Japanese Nohsan 1984 and 1985 guidelines GLP Test Material: MCPA-thioethyl (Purity: IUCLID technical dossier) Induction: 5% in paraffin oil/ Challenge: 25% in paraffin oil.	At 24 and 48 hours after removal of test substance for challenge, no abnormalities were observed at the application sites for animals induced/ challenged with MCPA-thioethyl. Under the conditions of this test, MCPA-thioethyl is not a dermal sensitiser.	Sugiya, 1985 M-CA 5.2.6

In a Magnusson and Kligman (M+K) Maximisation test with male Guinea pigs, there were no dermal reactions at challenge and re-challenge; therefore MCPA-thioethyl is not a skin sensitiser under the conditions of this test.

Comments received during public consultation

No comments received.

Assessment and comparison with the classification criteria

It is difficult to assess via the original study by Sugiya (1985), whether the doses for induction and challenge are set too low, primarily because of inadequate reporting. According to the test guideline, the concentration for the induction phase should cause mild to moderate skin irritation. This is not considered to be the case with the study by Sugiya, 1985.

No studies have been performed on MCPA-thioethyl, 10g/L preparation. Several studies have been conducted on formulations of salts of MCPA. All of these studies show no potential for skin sensitisation. The overall picture from the data available, shows no potential for skin sensitisation for MCPA-thioethyl.

Overall, RAC considers **MCPA-thioethyl not to warrant classification as a skin sensitiser**.

RAC evaluation of specific target organ toxicity– repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

Repeat dose toxicity studies have been conducted in the rat, mouse, rabbit and dog.

In the rat, the main findings were in the kidney and spleen and haematological parameters; in the MCPA 90-day rat study (Kirsch, 1985) there was increased kidney weights at 150 ppm (12 mg/kg bw/d) and above, although this was not linked to histopathological changes. In the Morrow (1974; IBT study, not considered by RAC) study with MCPA-thioethyl, splenic haemosiderin pigments were evident at 150 mg/kg bw/d and animals were anaemic. Kidneys were reported to be discoloured, but there was no histopathological correlate.

The Shirakawa (1973) study with MCPA-thioethyl reported atrophy of splenic lymphatic follicles, decreased spermatogenesis and atrophy of nerve cells in the spine and brain stem at 300 ppm (19 mg/kg bw/d) and above. The neurotoxicity study (90 days) (Mellert *et al*., 1994b) reported reduced grip strength in rats at 2500 ppm (177 mg/kg bw/d). The main change in this study was evidence of haemolytic anaemia at 2500 ppm (177 mg/kg bw/d). Kidney weights were significantly increased at 500 ppm (34 mg/kg bw/d) and above, but there was no histopathology. There was increased lipid in adrenals at 177 and 34 mg/kg bw/d. Data from the interim kills from the carcinogenicity studies confirmed a haemolytic anaemia and splenic congestion at high doses (approximately 78 mg/kg bw/d).

In the mouse studies (both conducted with MCPA-thioethyl) Morrow (1974; IBT study, not considered by RAC) reported increased splenic haemosiderin deposits at 150 mg/kg bw/d, whilst Shirakawa reported changes in the cranial nerve system of female mice (only) at 1000 ppm (equivalent to 150.3 mg/kg bw/d). The data from the interim kills of the mouse carcinogenicity studies is limited and does not provide any relevant information for consideration of STOT RE classification.

In the dog, reduced/loss of body weight, decreased liver and kidney function with degenerative/ regenerative changes in the liver, kidneys and gastro-intestinal tract were seen at 48 mg/kg bw/d (Reuzel, 1980). At 12 mg/kg bw/d, kidney function was affected, prostate weight was lower, there was a slight to moderate increased incidence of bile duct proliferation and an increased incidence of mononuclear cells in the liver. Kidney function was also decreased at 3 and 12 mg/kg bw/d. In the 2-year study, the main effects were in the liver and kidney, with hepatic extra-medullary haemopoiesis and pigmentation in the proximal tubules of the kidney at 5 and 25 mg/kg bw/d.

No treatment-related systemic toxicity was observed in the rabbit (sub-acute dermal).

Comments received during public consultation

One MSCA commented that classification as STOT RE Category 2 could be triggered. Based on the most reliable studies, kidney effects (effect on organ weight supported by clinical chemistry) were observed in the range of guidance value both in rats and dogs. As regard severity, in the absence of numerical data and/or of results in tabular format, it is difficult to assess the magnitude of the effects reported.

Regarding the 90-day dog study, it cannot be excluded that the severe clinical symptoms observed in 7/8 high dose dogs were consecutive of renal failure.

Another MSCA proposed that the STOT RE classification would mainly be based on effects on the nervous system in a 90-day feeding study with Wistar albino rats (Shirakawa, 1973) that was performed with MCPA-thioethyl. The critical effects consisted of atrophy of nerve cells in the spine

and brain stem, more pronounced in females, and reduced spermatogenesis, even at doses below the guidance value of 10 mg/kg bw per day. This would even justify category 1 (H372). An impact on spermatogenesis is in line with lower testis weights in the more recent neurotoxicity study of Mellert et al. (1994) with MCPA which were observed at 500 ppm (34 mg/kg bw/day) and above. Effects on spermatogenesis were seen in this study only above the classification limit but, on the other hand, MCPA thioethyl might be more toxic as suggested, e.g., by a higher acute oral toxicity (LD50 450 mg/kg bw as compared to 962 mg/kg bw for MCPA) or lower NOAELs in the short-term studies.

Immunotoxicity:

Pistl *et al*. (2003) investigated the immunotoxic potential of MCPA (purity 99.1%) (and seven other pesticides) in isolated sheep leukocytes at concentrations of 10^{-1} to 10^{-6} mol/L. Cytotoxicity (measured as a decrease in spontaneous leukocyte migration) occurred at 10^{-1} mol/L (16 cm^2 versus 27.6 cm^2 in the controls; $P < 0.01$). Immunotoxicity (measured as a decrease in lymphocyte activation with phytohaemagglutinin) occurred at concentrations ranging from 10^{-2} to 10^{-6} mol/L ($P < 0.001$). MCPA did not suppress the metabolic activity of sheep phagocytes in the iodonitrotetrazolium reductase test.

Even though a particular vulnerability of dogs to this class of herbicides is under discussion, the rather severe effects on several organs (blood, liver, kidneys, eyes) observed in this species generally support the need for a STOT RE classification.

These issues have been discussed extensively in the CLH dossier and STOT RE 2 (H373) is suggested.

Assessment and comparison with the classification criteria

The following treatment related effects that could be relevant for the STOT RE classification are evaluated among the data for the substance:

Haematological Parameters

A number of studies in the rat showed changes in haematological parameters indicative of anaemia. In the rat, there was evidence of haemolytic anaemia at 78.7 mg/kg bw/d at weeks 13, 26 and 52 weeks (Maita, 1988). In the sub-acute toxicity study (Mellert *et al*., 1994b) a macrocytic anaemia was reported at 177 mg/kg bw/d. There was no consistent evidence for anaemia in the mouse, dog or rabbit.

A summary of the findings in the studies is shown in the table below:

Haematological parameters					
Days	**Species**	**LOAEL**	**Effect**	**GLP**	**Ref. /year**
Carc. 1 y interim	Fischer rats	78,7 mg/kg bw/d	Week 13, 26 and 52 (haemolytic anaemia).	Yes	Maita, 1988
90 days	Rats (Thom)	177 mg/kg bw/d	Macrocytic anaemia.	(yes)	Mellert, 1994

According to the criteria given by ECB/JRC (written by Muller *et al*., 2006; *Hazard classification of chemicals inducing haemolytic anaemia: An EU regulatory perspective*, a reduction in Hb at or above 20% should be considered as evidence for marked organ dysfunction. This is regarded as a stand-alone criteria for classification while a Hb reduction at or above 10 % and indicators of

dysfuntions or organ damage are evident. Reduction in haematocrit should also be considered as indicators for anaemia.

The 2-year study with interim data by Maita (1988) with MCPA-thioethyl provide the best dataset for this endpoint. The following values for Hb is found for 13 weeks interim:

13 weeks interim (data for haemaglobin g/dl)				
Gender / dose	0 ppm	20 ppm	200 ppm	2000 ppm
Males	16.3	16.5	16.6	15.7
Females	17.2	17.1	16.8	16.1
13 weeks interim (data for haematocrit %)				
Gender / dose	0 ppm	20 ppm	200 ppm	2000 ppm
Males	50.7	51	51.4	48.9
Females	53.2	53.4	52.5	50.4

The haemolytic anaemia at week 13 or week 26 and 52 in the carcinogenicity study at the highest dose of 78.7 mg/kg bw/d was found to be a reduction of Hb of only 3-4% and was unaccompanied by haemosiderosis in the spleen, liver or kidney and is considered not to indicate significant haemolytic anaemia and therefore, no classification is warranted.

Spleen

Haemosiderin deposits were seen in the 90-day rat study (Shirakwa, 1973) at 57 mg/kg bw/d and above. This study was pre-GLP and before the establishment of recognised regulatory study protocols, thus whilst they are considered to offer useful additional information, the results must be interpreted with some caution. In the more recent GLP and regulatory compliant 90-day rat study with MCPA, (Kirsch, 1985), there was no evidence for haemosiderin deposits at the top dose equivalent to 37 mg/kg bw/d; similarly there was no evidence of spleen effects in the sub-chronic neurotoxicity study (Mellert *et al*., 1994) at the top dose equivalent to 177 mg/kg bw/d. At the 52 week kill in the rat carcinogenicity study (Maita, 1988) the top dose of 2000 ppm (equivalent to 78 mg/kg bw/d) did show splenic congestion and dilatation of sinuses. There was no evidence for spleen effects in the dog or rabbit.

The evidence for consideration for classification is, therefore not consistent. There was no evidence of spleen effects in the 90-day study, but there was evidence of an effect at the interim kill in the carcinogenicity study at 78.7 mg/kg bw/d. This was above the guidance value according to the CLP criteria for Category 2 classification for 1 year data ($2.5 < C \leq 25$ mg/kg bw/d) and therefore no classification is warranted.

Kidney

Kidney weights were increased at 12 mg/kg bw/d and above in the Kirsch *et al*. (1985), 90-day rat study, and for males in the sub-acute neurotoxicity study (Mellert *et al*., 1994) at 34 mg/kg bw/d. In the 90-day dog study (Reuzel *et al*., 1980) kidney function was reported to be affected at 3 and 12 mg/kg bw/d. None of these changes were accompanied by pathological findings. In the 48 mg/kg bw/d the increased kidney weight was accompanied by morphological changes in 3/8 dogs and by an increase of epithelial cells in the urine in 2/8 dogs. Signs of regeneration of tubular epithelium in the intercortico-medullary layer were seen in 3/8 dogs. The glomerulus filtration rate was affected by increased creatinine values, phenolred retention and increased plasma urea values supporting evidence of renal damage.

Later in the process, an additional package of data was received by the applicant and contained two 90-day repeated dose toxicity (RDT) studies on dogs (Hellwig *et al*., 1995; Sadlonova *et al*.,

2006 and Muckova 2005; the two latter based on the same data set). In Hellwig *et al*. (1995), 8 dogs in each dose group (4/sex) were administered 20 ppm, 80 ppm or 360 ppm MCPA DMA salt for 110-118 days. At 360 ppm (11.8 mg/kg bw/d) there was an increase in ALAT, urea and creatinine in both sexes. In the Sadlonova *et al*. (2006) and Muckova (2005), the dogs received 0, 1, 5, 15 mg/kg bw/d MCPA for 90 days. Increase in creatinine and urea were observed in dogs of all dose groups. In the high dose group an increase in glucose was seen. No histopathological changes were seen, and the observed changes were reversible.

RAC considers that MCPA-thioethyl do not fulfill the requirement for classification for STOT RE based on the effects in clinical chemistry seen in the kidney parameters, which were reversible. The morphological changes in the epithelium in the kidney seen in the dog study by Reuzel *et al*. (1980) at the highest dose of 48 mg/kg bw/d are not considered to be adverse in relation to the STOT RE classification. There is no information about reversitility when the dogs died or were killed during the study.

A summary of the findings in the studies is shown in the table below:

Kidney					
Days	**Species**	**LO(A)EL**	**Effect**	**GLP**	**Ref./year**
90	Wistar Rat	12 mg/kg bw/d	Increased weights	Yes	Kirsch *et al*., 1985
90	Rat males	34 mg/kg bw/d	Increased weights	(Yes)	Mellert *et al*., 1994
90	Beagle dog	48 mg/kg bw/d	Regeneration of tubular epithelium in the intercortico-medullary layer.	No	Reuzel *et al*., 1980
90	Beagle dog	2.6, 11.8 mg/kg bw/d	Increase in urea and creatinine	Yes	Hellwig *et al*., 1995
90	Beagle dog	(1), 5, 15 mg/kg bw/d	Increase in urea and creatinine	No	Sadlonova *et al*., 2006
90	Beagle dog	1, 5, 15 mg/kg bw/d	Increase in creatinine and (glucose (15mg)).	Yes	Muckova, 2005

Nervous System

The primary study for consideration of effects on the nervous system is the sub-acute study in rats (Mellert *et al*., 1994); apart from decreased grip strength at the top dose of 177 mg/kg bw/d (which may have been a consequence of the significant decreased bodyweight effect), there was no evidence of neurological changes.

Summary of the studies:

Nervous System					
Days	**Species**	**LO(A)EL**	**Effect**	**GLP**	**Ref./year**
90	Rat	177 mg/kg bw/d MCPA	Grip strength	(Yes)	Mellert *et al*., 1994
90	Wistar rat	8.2 mg/kg bw/d MCPA-thioethyl	Minimal atrophy of nerve cells in the spine and brain stem.	No	Shirakawa, 1973
90	Mouse	150 mg/kg bw/d females.	Changes in the cranial nerve system.	No	Shirakawa, 1973

Detailed information related to the effects seen in mice in the nervous system (Shirakawa, 1973):

Dose/effect	**0 ppm**	**30 ppm**	**100 ppm**	**300 ppm**	**1000 ppm**
Mice	0/10	0/10	0/10	2/10	0/10
Slight atrophy of nerve cell	0/10	2/10	1/10 (ventricornual)	0/10	2/10
Mice	0/10	0/10	1/10	0/10	0/10
Atrophy of cortex nerve cell	0/10	0/10	0/10	0/10	0/10
Mice Nissl's body	0/10	0/10	0/10	0/10	0/10
	0/10	0/10	1/10	1/10	1/10

Detailed information related to the rats and effects in the nervous system (Shirakawa, 1973):

Doses / effects	**0 ppm**	**30 ppm**	**100 ppm**	**300 ppm**	**1000 ppm**
Rats	0/10	0/10	0/10	2/10	3/10
Spinal cord atrophy	0/10	0/10	1/10 (ventricournual nerve cell)	3/10 (ventricournual nerve cell)	2/10 (1 ventricournual nerve cell)
Rats	0/10	0/10	0/10	0/10	6/10
Brain stem – tigrolysis of some nerve cells	0/10	0/10	0/10	0/10	0/10
Rats	0/10	0/10	0/10	0/10	0/10
Brain stem – Nissl's body	0/10	0/10	0/10	0/10	2/10

The 90-day rat study by Shirakawa (1973) reported minimal atrophy of nerve cells in the spine and brain stem at 8.2 mg/kg bw/d; the corresponding mouse study (Shirakawa, 1973) reported changes in the cells of profundus area of cerebral cortex in female mice at 150 mg/kg bw/d. In the light of the age of these studies (pre-GLP and the adoption of accepted regulatory protocols) and the poor reporting (only the illustrated slides without any grading of severity), priority is given to the results from the Mellert *et al*. (1994b) study. No nervous system effects were reported in the rabbit or dog.

No classification for STOT RE effects on the nervous system is warranted.

Testes

In the 90 day-rat study (Shirakawa, 1973) decreased spermiogenesis was reported at 8.2 mg/kg bw/d. In the sub-acute neurotoxicity study (Mellert *et al*., 1994b), lower testes weights were recorded at 34 mg/kg bw/d and above and at the top dose of 177 mg/kg bw/d there was severe to extreme atrophy of the testes with oligozoospermia and aspermia. No effects on sperm were reported in the Kirsch *et al*. (1985) rat study, or in the interim kill at 52 weeks in the Maita (1988) carcinogenicity study.

No effects were reported in mice, dogs or rabbits. A summary of studies describing effects on testes is shown in the table below:

Testes					
Days	**Species**	**LO(A)EL**	**Effect**	**GLP**	**Ref./year**
90	Wistar rat	8.2 mg/kg bw/d MCPA-thioethyl	Proliferation of spermiogenesis tends to decrease.	No	Shirakawa, 1973
90	Rat	34 mg/kg bw/d MCPA (testes weights)	Weights, severe to extreme atrophy of the testes with oligozoospemia and aspermia at 177 mg/kg bw/d	(yes)	Mellert *et al*., 1994b
90	Beagle dog	5 mg/kg bw/d MCPA	Relative weights of both testes were decreased in the males from the high dose group associated with focal testicular atrophy and loss of spermatogenic cells in the lobuli of testes.	No	Sadlonova/Muckova *et al*., 2005/6

No effects on sperm were reported in Kirsch et al 1985 or in the interim kill in the Maita 1988. No effects on sperm were reported in mice, dogs or rabbits.

Detailed information of spermiogenesis from Shirakawa (1973) in mice and rats is shown in the table below:

Doses/ Species	**0 ppm**	**30 ppm**	**100 ppm**	**300 ppm**	**1000 ppm**
Mice **Atrophy**	0/10	0/10	1/10	0/10	0/10
Mice **Decreased spermiogenesis**	0/10	0/10	1/10	0/10	1/10
Mice **Partial obstroction**	1/10	2/10	3/10	1/10	0/10
Rats **Decreased spermiogenesis**	0/10	0/10	5/10	0/10	5/10

As stated before, the effects reported in the rat by Shirakawa are poorly described without any detailed description and without grading of severity of the observed effects. However, the potential for MCPA-thioethyl and MCPA is supported by the effects seen in theGLP compliant Mellert *et al*. (1994b) study. The lower testes weights recorded in this study in the absence of evidence of functional or structural changes are considered not to represent significant target organ toxicity. Extreme to severe testicular atrophy and effects on sperm at 177 mg/kg bw/d were associated with significant systemic toxicity (27-21% decreases in body weight; 42 and 48% decrease in body weight gain) and therefore are not relevant for consideration of classification.

Additional studies were submitted during the CLH process. In a publication by Sadlonova I/Muckova *et al., 20*05/2006, a study was performed to investigate the toxicity of MCPA after repeated treatment according to OECD TG 409 with daily doses of 0, 1, 5 or 15 mg/kg bw/d during 90 days. The study showed a decrease in the relative weights of both testes in the males from the high dose group associated with focal testicular atrophy and loss of spermatogenic cells in the lobuli of testes.

MCPA (mg/kg bw/d)	Testis right (g.)	Testis left (g.)
Control	1.06±0.10	1.05±0.14
1	1.09±0.13	1.11±0.15
5	0.94±0.07	0.98±0.10
15	0.78±0.11*	0.73±0.09*

*P<0.05.

In addition, effects on the testes should be considered for classification as a reproductive toxicant. However, in two reproduction toxicity studies (one- and two-generation reproduction studies) neither MCPA-thioethyl nor MCPA was found to induce any effects on fertility, reproduction, pregnancy outcome or litter parameters in the rat. Consequently MCPA-thioethyl does not meet the criteria for classification as STOT RE based on effects on testes.

Liver

In the sub-acute neurotoxicity study (Mellert, 1994b) at 177 mg/kg bw/d there was a liver weight increase and pathology showed marker hepatocellular cytoplasmic eosinophilia and granular cytoplasm. The effect dose were outside the Guidance Value Ranges: 10 < C ⩽ 100 mg/kg bw/d and consequently no classification is warranted.

In the 90-day dog study (Reuzel *et al*., 1980), at 12 mg/kg bw/d there was a slight increase in the incidence and degree of infiltrates of mononuclear cells in the liver and at 48 mg/kg bw/d there were degenerative/ regenerative changes.

A later submission of a 90 days dog study by Muckova/Sadlonova et al. 2005/6 was to investigate the toxicity of MCPA after repeated treatment according to OECD 409 with daily doses of 0, 1, 5 or 15 mg/kg bw/d during 90 days. Increase in ALT, urea was observed in the middle and high dose group. Decreased ALP associated with focal hepatocellular necrosis, inflammatory changes and mononuclear nodules were observed in high dose gr predominantly in males.

Summary of studies describing effects in the liver:

Liver					
Days	**Species**	**LO(A)EL**	**Effect**	**GLP**	**Ref./year**
90	Rat males	177 mg/kg bw/d MCPA	Weights increased , hepatocellular cytoplasmic eosinophilia	(Yes)	Mellert et al 1994
90	Beagle Dog	12 mg/kg bw/d MCPA	Slight increase in the incidence and degree of infiltrates of mononuclear cells. In the 48 mg/kg/d histopathological changes in the liver.	No	Reuzel et al. 1980
90	Beagle dog	1, 5, 15 mg/kg bw/d MCPA	↑ ALT, ↓ ALP, focal hepatocellular necrosis, inflammatory changes and mononuclear nodules were observed commonly in males in the high dose gr.	(Yes)	Muckova/Sadlonova 2005/6

The effects at 12 and particularly at 48 mg/kg bw/day in the dog study showed pronounced histological liver changes in all dogs. These comprised of focal and diffuse liver cell dissociation (6/8), focal necrosis (5/8) and scattered single cell necrosis; in most cases their changes were accompanied by infiltrates of mononuclear inflammatory cells, abnormal liver cells with distinct cytomegaly and karyomegaly, centrilobular liver cell degeneration and bile duct proliferation. Mitotic figures were numerous in some cases. All animals in the high dose also showed distinctly

jaundice, bilirubin excretion in the urine, yellow faces, bilirubinaemia indicating clear dysfunction of the liver.

Specific target organ toxicity (repeated exposure) applies where significant health effects are reported which are considered to impair function, both reversible and irreversible. Potential effects are classified under Category 2; 10 < C ⩽ 100 mg/kg bw/day in 90 day oral studies.

RAC consider that MCPA-thioethyl meet the requirement for classification for STOT RE 2, based on the severe effects observed in the liver in the 90 days dog study by Reuzel et al. 1980 in the highest dose of 48 mg/kg bw/d.

Gastro-Intestinal Tract

In the 90-day dog study (Reuzel et al, 1980) at 48 mg/kg bw/day, the occurrence of considerable quantities of blood in the faeces indicated that the gastro-intestinal tract was affected. This was also confirmed by morphological findings in the organ. There were haemorrhages in the intestine and stomach; pathology revealed degenerative/ regenerative changes in the GI tract in 3/8 dogs.

The gross pathology shows that there was haemorrhage to the buccal cavity, stomach and intestines and presence of faecal blood. This could be due to the topical effect of the acid MCPA on the mucous membranes and gut lining. In addition, the dose of 48 mg/kg bw/d exceeded the MTD, 7/8 of the dogs showed severe clinical signs, one dog died and six others were sacrificed in-extremis.

RAC consider that the observed effects may be due to the acidity of MCPA and these effects cannot be directly transferred to the thio-ester. Therefore no STOT RE classification for the observed effects in the GI tract is justified for the MCPA-thioethyl.

Lethality

In the 90-days study (Reuzel et al. 1980) the highest dose of 48 mg/kg bw/d was very toxic to the dog. One out of 8 dogs died and six others were killed in a moribund state at 48 mg/kg bw/day.

Discussions as to whether dogs can be used to predict the toxicity of the phenoxyacetic acids have taken place in the evaluation of several phenoxyacetic acids. Toxicokinetic data show that for dogs, a higher plasma half-life may result in higher AUC. Therefore dogs may have a higher susceptibility to the toxic effects of phenoxyacetic acids than other species including humans. The discussion is mostly based on the review of literature by Timchalk: *Comparative inter-species pharmacokinetics of phenoxyacetic acid herbicides and related organic acids. Evidence that the dog is not a relevant species for evaluation of human health risk. Toxicology. 2004 Jul 15;200(1):1-19.* However, this discussion was mostly related to the phenoxyacetic acid 2,4-D. The specific MCPA pharmacokinetic parameters for plasma half-lives were calculated to 5.8 h for the rat, 46 h for the dog and 11h for the human (Timchalk, C. 2004). RAC does not assess the individual differences in half-lives as crucial higher susceptibility to the toxic effects in dogs seen in Reuzel et al 1980.

However, RAC concluded the observed GI tract lesions may be due to the acidity of MCPA and these effects cannot be directly transferred to the thio-ester. Clinical observations reported in the study by Reuzel 1980, where it is stated that there were occurrence of considerable quantities of blood in the faeces in the 48 mg/kg/d dose gr. RAC considers that the lethality may be secondary to the extremely poor clinical conditions of the dogs especially based on the damage to the GI tract.

RAC consider that the lethality caused by MCPA could be related and secondary to the observed effects in the GI tract. This may be due to the acidity of MCPA and these effects cannot be directly transferred to the thio-ester. Therefore no STOT RE classification for lethality is justified for the MCPA-thioethyl.

Summary of STOT RE classification

The results of studies (originally submitted and from the targeted public consultation) indicated unequivocal adverse effects on the liver. Relevant clinical chemistry parameters and/or histopathological evaluation were similar in all studies on dogs and the NOAEL values of these studies are very close to each other.

Study			Pathological changes		
	Test item	NOAEL mg/kg bw/d	Dose mg/kg bw/d	Clinical chemistry	Histopathology* Liver
Hellwig, 1995	**MCPA-DMA salt**	**0.7**	11.8	↑ ALT,↓ ALP	Yes
Reuzel, 1980	**MCPA**	**1**	3, 12, 48**	No measurement	Yes
Sadloňová/Muckova, 2005/6	**MCPA**	**< 1**	(1), 5, 15	↑ ALT, ↓ ALP	Yes (15 mg/kg)

*Histopathology Yes-the presence of histopathological changes

**Lethality, marked overall dog intoxication

ALT increase and ALP decrease indicate hepatic cells damage, as confirmed by findings of necrosis and inflammatory changes in the hepatic tissue. Therefore, the affected target organ relevant for classification with STOT RE is the liver.

RAC consider that MCPA-thioethyl meets the requirement for classification for **STOT RE 2; H373, based on the severe effects observed in the liver** in the 90 days dog study by Reuzel et al. 1980 in the highest dose of 48 mg/kg bw/d.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Summary of studies:

Method	Results and Remarks	Reference
Bacterial assay for gene mutation Rec-assay with *Bacillus subtilis.* Positive control, mitomycin C; negative control Kanamycin Reverse mutation *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 and TA100 and *Escherichia coli* WP2 hcr. Positive controls; 2-aminoanthracene Host-mediated study *Salmonella typhimurium* G46 in mice. Positive control dimethylnitrosamine (DMN). Guideline: similar to OECD 471 GLP- not stated Test Material: MCPA-thioethyl.	Rec-assay: MCPA-thioethyl produced similar inhibition zones to the negative control kanamycin. The positive control, mitomycin C induced a marked difference between the lengths of the inhibition zones. Reverse-mutation assay: the positive controls AF-2; β-propiolactone; 9-aminoacridine and 2-nitrofluorene induced marked reverse mutations in the relevant strains tested. 2-aminoanthracene was activated by the S-9 Mix and was mutagenic for TA98, TA100, TA1535, TA1537 and TA1538. MCPA-thioethyl did not induce any increase in revertant colonies in any strains in the presence or absence of the S-9 Mix up to the top dose of 1000ug/plate. Host-mediated assay: There was no significant increase in the mutation frequency with MCPA-thioethyl compared to the control. The positive control, DMN, induced a significant increase in the mutation frequency.	Shirasu, no date

(Purity: IUCLID technical dossier)	It was concluded that under the conditions of these studies, MCPA-thioethyl was negative in the rec-assay and reverse mutation assay (with and without metabolic activation) and negative in the host-mediated assay.	
In vitro -chromosome test in mammalian cells Chinese Hamster V79 cells Guideline: similar to OECD 473 GLP – not stated Test Material: MCPA-thioethyl. (Purity: IUCLID technical dossier) Positive control – mitomycin C (-S9) and dimethylnitrosamine (+S9). Cells treated in the range of 0.6 to 2.4 mg/mL, with and without metabolic activation (S9). 100 metaphase chromosomes examined at each dose level.	There was no inhibition of cell growth up to the highest concentration tested, which was a limit dose of 10mM. MCPA-thioethyl was incubated with V79 cells for 24 hours (-S9) and harvested, or 5 hours +S9, and then harvested after a further 19 hours. MCPA-thioethyl did not induce chromosomal aberrations at any of the concentrations tested. The positive controls induced clear increases in chromosomal aberrations. It was concluded that under the conditions of this study, MCPA-thioethyl was negative in this in vitro mammalian chromosome assay.	Shibuya, 1984
In vitro Mammalian cell gene mutation L5178Y mouse lymphoma cells Guideline: OECD 476 GLP Test Material: MCPA-thioethyl. (Purity: IUCLID technical dossier) Cells treated in range of 0.3 to 33 µg/mL in the absence of S9-mix with a 3 and 24 hour treatment period and in the presence of S9-mix with a 3 hour treatment period. Positive control agents were ethyl methanesulphonate (EMS), and dimethylnitrosamine (DMN)	MCPA-thioethyl was tested up to concentrations of 17 and 33 µg/mL in the absence and presence of 8 % (v/v) S9-mix, respectively. Incubation time was 3 hours. Toxicity was observed at these dose levels in the absence and presence of S9-mix. In the second experiment, MCPA-thioethyl was tested up to concentrations of 33 µg/mL in the absence and presence of 12 % (v/v) S9-mix.Incubation time was 24 hours in the absence of S9, and 3 hours in the presence of S9. Toxicity was observed in the presence of S9. MCPA-thioethyl did not induce a significant increase in the mutant frequency in the absence or presence of S9 metabolic activation in either experiment. Mutant frequencies in cultures treated with positive control chemicals increased significantly in both the first and second experiments. It was concluded that MCPA-thioethyl is not mutagenic in the mouse lymphoma L5178Y test system under the experimental conditions described in this report.	Verspeek-Rip, 2002
In vivo studies in somatic cells Micronucleus test in bone marrow cells Mouse: NMR1 BR Guideline: OECD 474 GLP Test Material: MCPA-thioethyl. (Purity: IUCLID technical dossier) 5/ sex/ group; vehicle control, positive control (50 mg/kg bw cyclophosphamide), 125, 250 and 500 mg/kg bw MCP-thioethyl by oral gavage. Micronuclei counted in 2000 polychromatic erythrocytes, at 24 and 48 hours after dosing.	No increase in the frequency of micronucleated polychromatic erythrocytes in any of the MCPA-thioethyl treated groups. The positive control (cyclophosphamide) induced a statistically significant increase in micronuclei. There was a significant decrease in the ratio of polychromatic to normochromatic erythrocytes, (indicating a toxic effect of MCPA-thioethyl on erythropoiesis), in animals treated with 500 mg MCPA-thioethyl/kg body weight for 48 hours and in animals in the positive control group. MCPA-thioethyl was not mutagenic in the micronucleus test under the experimental conditions described in this report.	Meerts, 2002

The mutagenicity of MCPA-thioethyl was examined in a series of three bacterial genotoxicity studies, two mammalian cell in vitro assays (chromosomal test in Chinese hamster V79 cells and L5178Y mouse lymphoma cell gene mutation) and in an in vivo mouse micronucleus assay in bone marrow). MCPA-thioethyl was negative in all assays examined. Based on the negative findings in *in vitro* and *in vivo* mutagenicity studies, MCPA-thioethyl is not mutagenic. MCPA-thioethyl does not, therefore, warrant classification for genotoxicity or mutagenicity based on the negative findings.

Comments received during public consultation

No comments received related to this endpoint.

Assessment and comparison with the classification criteria

RAC agrees with the dossier submitter, based on the negative findings in *in vitro* and *in vivo* mutagenicity studies, that MCPA-thioethyl **does not warrant classification as a germ cell mutagen**.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

Summary of studies:

Method	Results and remarks	Reference
Rat: Fisher F34/DuCrj Carcinogenicity- chronic toxicity (24 months) Guideline: OECD 453 GLP Test Material: MCPA-thioethyl. (Purity: IUCLID technical dossier) 80 male and 80 females/ group 0, 20, 200 and 2000 ppm in diet, equivalent to 0, 0.95, 9.3, and 98.5 mg/kg bw/day. 10/sex grp for haematology at 13 weeks. 10/sex/grp for haematology, clinical chemistry and pathology at 26, 52 and 78 weeks. Clinical pathology on 10/sex/grp at termination.	No evidence of carcinogenic effect following treatment with MCPA-thioethyl. **2000 ppm (98.5 mg/kg bw/day):** decreased incidence of mononuclear cell leukemia in both sexes, associated with decreased mortality in males. Decreased body weight gain throughout the study (3-6% for males, 3-12% for females. Anaemia in both sexes. High levels of GOT, GPT, ALP and BUN and a low level of glucose were found in both sexes. Increased thyroid weight in both sexes, an increasing trend of kidney weights in males, and increased spleen weights in females. Males and females showed splenic congestion and increased brown pigment deposition in the renal tubular cells. Increased incidences of micro-granuloma of the liver and bone marrow and periosis lesions in the thyroid and skin were attributed to treatment. **200 ppm (9.3 mg/kg bw/day):** males had slightly lower body weights (2-4%) during the first year. Increased thyroid weights in both sexes. A higher incidence of microscopical lesions and increased brown pigment deposition in the renal tubular cells was seen in males. **20 ppm (0.95 mg/kg bw/day):** no adverse effects **No evidence of carcinogenicity. The NOEL for toxicity was 0.95 mg/kg bw/day.**	Maita, 1988
Rat: Wistar Carcinogenicity- chronic toxicity	No compound-induced benign or malignant tumour incidence was noted at any dose level.	Kirsch et al. 1988

(24 months) Guideline: OECD 453 GLP Test Material: MCPA (Purity: IUCLID technical dossier) 50 male and 50 females/ group, main study 2 satellite groups of 10 and 15 rats/ sex/group for urinalysis and heamatology; Satellite grp II sacrificed after 12 months/ 0, 20, 80 and 320 ppm in diet, equivalent to 0, 1.25, 5, and 20 mg/kg bw/day. Histopathology on all animals	**320 ppm (20 mg/kg bw/day)**: reduced body weight gain of up to 9% in males. Plasma ALT significantly increased in females at 12, 18 and 24 months. Decreased triglycerides in both sexes. At autopsy, progressive nephropathy associated with increased kidney weights and increased haemosiderosis in the spleen. The relative liver weight of the females was significantly decreased compared to control. **80 ppm (5 mg/kg bw/day):** sporadically increased values for triglyceride in both sexes and ALT activity in females **20 ppm 1.25 mg/kg bw/day):** relative liver weight of females was significantly reduced. Regarded as not treatment-related as no decrease at 80 ppm, and no associated histopathology. **No evidence of carcinogenicity. NOEL for toxicity was 20 ppm (equivalent to approximately 1.3 mg/kg bw/day).**	
Mouse: ICR (Crj:CD1) Carcinogenicity- chronic toxicity (18 months) Guideline: OECD 451 GLP Test Material: MCPA-thioethyl. (Purity: IUCLID technical dossier) 70 male and 70 females/ group 0, 30, 300, 1500 ppm in diet, equivalent to 0, 2.8, 29.3, and 151 mg/kg bw/day 20/sex/ group terminated at 52 weeks At 52 and 78 weeks, blood smears taken from 10/sex/group. Histopathology on all animals.	No evidence of carcinogenic effect following treatment with MCPA-thioethyl. **1500 ppm (151 mg/kg bw/day):** decreased mean body weight (< 10%) throughout the treatment period; statistically significant decrease in males from week 1 to week 16 and in females from week 3 to week 52. Food efficiency was 10% and 19 % lower for males and female, respectively, for the first 13 weeks compared to controls. At autopsy, signs of hepatotoxicity (dark coloured livers and increased brown pigment deposition in Kupfer cells) **300 ppm (29.3 mg/kg bw/day):** slight but consistent decrease in body weight and food efficiency. **30 ppm (2.8 mg/kg bw/day):** No adverse effects. **No evidence of carcinogenicity. NOEL for toxicity (based on limited parameters examined) was 30 ppm (equivalent to 2.8 mg/kg bw/day).**	Harada, 1992
Mouse: B6C3F1 Carcinogenicity (24 months) Guideline: OECD 451 GLP Test Material: MCPA. (Purity: IUCLID technical dossier) 50 male and 50 females/ group plus satellite groups of 10/ sex/ group 0, 20, 100, 500 ppm in diet Satellite group used for heamatology and interim sacrifice at week 52 Histopathology on all animals	There were no treatment-related effects in mortality, state of health, body weight or food consumption in any group. Haematology also revealed no indications of a substance-induced effect. There was no evidence of a carcinogenic effect. **500 ppm approximately 80 and 100 mg/kg bw/day for males and females respectively):** Males showed intermittent reduction of body weight gain from week 3 up to 1 year. An increase in the Howell-Jolly bodies in the females (5/10 animals) could be indicative of a marginal adverse effect of the test substance on the red blood cells; some animals of this test group showed other morphological changes of the erythrocytes. There were signs of nephropathy. Absolute and relative kidney weights were increased in female rats and histopathology revealed an increased incidence of intra-tubular calcification and hyaline casts in both sexes. Tubular epithelial hyperplasia was observed in the males. Significant decrease in heart and testes weights, but no histopathological correlate.	Kűhborth et al, 1988

	100 ppm (approximately 16 and 20 mg/kg bw/day for males and females respectively): Males showed intermittent reduction of body weight gain from week 3 up to 1 year. At autopsy, significant decrease in heart weight, but no histopathological correlate. **20 ppm (approximately 3 and 7 mg/kg bw/day for males and females respectively** no toxicological effects. **No evidence of carcinogenicity. The NOEL for chronic toxicity was 100 ppm (approx. 16 mg/kg bw/day for males and approx. 20 mg/kg bw/day for females**	

Four rat and mouse studies investigating the carcinogenic potential of both MCPA-thioethyl and MCPA are available for consideration. All four studies reported no increase in the number or type of benign or malignant tumours at any dose level tested. A limited number of epidemiological studies have been conducted on the effects of MCPA and related chlorophenoxy compounds, however, the evidence for carcinogenicity is inconclusive. Available studies have dealt with multiple exposures to mixtures of chlorophenoxy herbicides, other pesticides, as well as, other organic compounds. The results were difficult to interpret, and the studies are considered limited for several reasons, such as the lack of consideration of confounding factors and small sample size. As there was no evidence of a carcinogenic effect for either MCPA-thioethyl or for MCPA in well conducted rat and mice studies, no classification for carcinogenicity is warranted.

Comments received during public consultation

No comments received for this endpoint.

Assessment and comparison with the classification criteria

As there was no evidence of a carcinogenic effect for either MCPA-thioethyl or for MCPA in well conducted rat and mice studies, RAC agrees with the dossier submitter that **no classification for carcinogenicity is warranted**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Summary of studies:

Method	Results and Remarks	Reference
2-generation reproduction (2 litters per generation) Rat: Crl:CD®(SD)BR Guideline: US EPA GLP: Yes Test Material: MCPA (Purity: IUCLID technical dossier) Treatment: continuous in the diet at 0, 50, 150 or 450 ppm F0 - 25 males and 25 females per group,	**450 ppm (approximately 40 mg/kg bw/day):** significant reduction of body weight from weaning through the premating period in the F1 adults of both sexes. Reduced pup body weight and weight gain. Gross pathological or histopathological examinations did not indicate any adverse effects. **150 and 50 ppm (approximately 12 and 4 mg/kg bw/day):** No effects on reproduction parameters and no systemic toxicity in parents or offspring. **The NOAEL for reproductive toxicity was 450 ppm (equivalent to approx. 40 mg/kg bw/day). The NOAEL**	Mackenzie, 1986

allowed to reach maturity and then mated to produce 2 litters. 25 male and 25 female rats/group selected from the second litter to produce the next generation. Study terminated following weaning of F2. Parental growth and condition recorded. Reproductive performance and litter parameters monitored. Necropsies on all parental rats and 10 pups of each sex/ group. Tissues examined in all control and high dose F0 and F1b adults.	**for parental toxicity was 150 ppm (equivalent to approx. 12 mg/kg/day). The NOAEL for pup toxicity was also 150 ppm.** It should be noted that the mg/kg equivalents are different in the DAR and the JMPR document. The figures presented here are taken from the JMPR document which contains a table of dose achieved.	
1-generation reproduction Rat: Alpk:AP_fSD Guideline: not stated GLP: not confirmed Test material: MCPA (Purity: IUCLID technical dossier) 12/ sex/ group 0, 450, 750 or 1000 ppm in diet (Doses reduced during lactation to avoid high doses to lactating dams and pups). Litters reared to weaning then 10 F1 pups/ sex/group selected for further 2 weeks of dosing at the higher rates. Reproductive performance assessed; pup survival and body weight recorded	**1000 ppm (88 mg/kg bw/day):** lower body weight pre-mating and gestation, lower food consumption. No effect during lactation. Pup body weights lower on day 29 of lactation. **750 and 450 ppm (67 and 38 mg/kg bw/day):** body weight lower for first 3 weeks. **The NOAEL for reproductive toxicity was 1000 ppm (approximately equal to 88 mg/kg bw /day.** **The NOAEL for parental toxicity was less than 450 ppm (approximately equal to 38 mg/kg bw/day).**	Milburn, 2004
Developmental Toxicity Rat: Wistar Imamichi Guideline: not stated GLP: Yes Test Material: MCPA-thioethyl (phenothiol) (Purity: IUCLID technical dossier) 23 dams/ group 0, 10, 40 and 160 mg/kg bw/day in 0.5% aqueous carboxymethylcellulose Oral gavage (gestation days 6-15) Termination day 21. Foetuses examined for external, visceral and skeletal abnormalities.	**160 mg/kg bw/day:** Decreased body weight gain and food consumption, increased water consumption. Increased maternal spleen weight, but no gross abnormality. Foetal weight decreased and ossification of sacral and caudal vertebrae reduced. No malformation. Slight foetal growth retardation occurred in the presence of maternal toxicity. **10 and 40 mg/kg bw/day:** No significant effects on dams or foetuses. **NOAEL for maternal and developmental toxicity was 40 mg/kg bw/day.**	Tauchi, 1984
Developmental Toxicity Rat: Wistar (Chbb:THOM(SPF)) Guideline: OECD 414 GLP: Yes Test Material: MCPA acid (Purity: IUCLID technical dossier) 22-24 dams/ group 0, 15, 60 and 120 mg/kg bw/day in 0.5% carboxymethylcellulose. Oral gavage (gestation days 6-15) Termination day 20. Foetuses examined for external, visceral and skeletal abnormalities.	**120 mg/kg bw/day:** Reduced food consumption and body weight gain in dams. Reduced foetal weight and decreased ossification of skull and sternebrae. Slight foetal growth retardation occurred in the presence of maternal toxicity. **15 and 60 mg/kg bw/day:** No significant effects on dams or foetuses. **The NOAEL for maternal and developmental toxicity was 60 mg/kg bw/day.**	Hellwig & Hildebrand, 1993a (Preliminary dose range finding study Hellwig, 1992a)
Developmental Toxicity Rat: Sprague Dawley (CD) Guideline: No	**125, 50 and 20 mg/kg bw/day:** No treatment-related findings. Small group size precludes definitive evaluation but when considered with the range-finding study, the results indicate that MCPA was neither teratogenic nor	Irvine, 1980a (Preliminary dose range finding study

GLP: No Test Material: MCPA (purity not stated) 5 dams/ group 0, 20, 50 and 125 mg/kg bw/day in 1% carboxymethylcellulose. Oral gavage (gestation days 6-15) Termination day 21. Foetuses examined for external, visceral and skeletal abnormalities.	embryotoxic.	Irvine & Tucker, 1978a)
Developmental Toxicity Rabbit: Japanese white Guideline: Japanese MAFF (1984) GLP: Yes Test Material: MCPA-thioethyl (Purity: IUCLID technical dossier) 16 dams/ group 0, 40, 80 and 160 mg/kg bw/day in 0.5% carboxymethylcellulose Oral gavage (gestation days 6-18) Termination day 29. Foetuses examined for external, visceral and skeletal abnormalities.	**160 and 80 mg/kg bw/day:** One female at each dose aborted. No other maternal effects, no developmental effects, no malformation. **40 mg/kg bw/day:** No significant effects on dams or foetuses. **The NOAEL for maternal toxicity was 40 mg/kg bw/day and the NOAEL for developmental toxicity was 160 mg/kg bw/day.**	Sakamaki, 1985
Developmental Toxicity Rabbit: Himalayan (Chbb:HM) Guideline: OECD 414 GLP: Yes Test Material: MCPA acid (Purity: IUCLID technical dossier) 13-14 dams/ group 0, 1, 15, 30 and 60 mg/kg bw/day in 0.5% carboxymethylcellulose Oral gavage (gestation days 7-19) Termination day 29. Foetuses examined for external, visceral and skeletal abnormalities.	**60 mg/kg bw/day:** Maternal toxicity (one death and one abortion), slight weight loss and reduced food consumption. No evidence of developmental effects. **30 mg/kg bw/day**: One abortion. No evidence of developmental effects. **15 mg/kg bw/day**: No significant effects on dams or foetuses. **The NOAEL for maternal toxicity was 15 mg/kg bw/day and for developmental toxicity the NOAEL was at least 60 mg/kg bw/ day.**	Hellwig & Hildebrand, 1993b (Preliminary dose range finding study Hellwig, 1992b)
Developmental Toxicity Rabbit: Dutch Belted Guideline: Not stated GLP: No Test Material: MCPA (purity not stated) 15-18 dams/ group 0, 5, 12, 30 and 75 mg/kg bw/day in 1% carboxymethylcellulose. Oral gavage (gestation days 6-18) Termination day 28. Foetuses examined for external, visceral and skeletal abnormalities.	**75, 30, 12 and 5 mg/kg bw/day:** Deaths occurred at and above 12 mg/kg bw/day in association with a respiratory infection. Post-implantation loss was higher at 75 mg/kg bw/day but foetal weight and crown–rump length were not reduced. There were no treatment-related external, visceral or skeletal malformations. The NOAEL for maternal toxicity was 5 mg/kg bw/day and for developmental toxicity the NOAEL was 30 mg/kg bw/day. **The possible confounding effect of respiratory infection on the study outcomes makes the conclusions on NOAEL's unreliable.**	Irvine, 1980b (Preliminary dose range finding study Irvine & Tucker, 1978b)
Developmental Toxicity Mouse: NMR1 Guideline: not stated GLP: not stated Test Material: MCPA (purity not stated) 13-34 dams/ group 0, 50, 100, 200, 300, 400 or 500 mg/kg bw/day in peanut oil	This applicant does not have access to the study report or data. However, the results are considered to be unreliable because: • the NMRI strain is reported to have a high background incidence of cleft palate (data not available) • the DAR reports that data on maternal toxicity such as clinical signs and mortality were reported with insufficient detail	Roll & Mattiaschk, 1983 (German publication)

Oral gavage (gestation days 6-15) Termination day 18. Foetuses examined for external, visceral and skeletal abnormalities.	• the authors note that the oral LD_{50} of MCPA for mice is 600 mg/kg bw; therefore, the higher dose levels were in the range of the cited LD_{50} value. **500, 400, 300 and 200 mg/kg bw/day:** Dose-dependent reduction in body weight at ≥200 mg/kg bw/day. Increased post-implantation loss ≥300 mg/kg bw/day. Foetal body weight reduced ≥200 mg/kg bw/day. Increased incidence of cleft palate and fused ribs at ≥200 mg/kg bw/day. **100 mg/kg bw/day:** Foetal body weight reduced. **50 mg/kg bw/day:** No maternal or developmental toxicity. The NOAEL for maternal toxicity was 100 mg/kg bw/day and the NOAEL for embryo/foetotoxicity was 50 mg/kg bw/day. **The study is considered by the DS to be unreliable.**	

No adverse effects on fertility or development were, according to the DS, observed at any dose levels evaluated.

Comments received during public consultation

No comments received for this endpoint.

Assessment and comparison with the classification criteria

Effects on fertility (multigeneration studies in rats and the 90 days RDT by Shirakawa 1973 and Mellert et al. 1994b)

The effects of MCPA (94.8%) on reproduction parameters and postnatal development of Sprague-Dawley rats were investigated in a two-generation (two litters per generation) study according to US EPA guidelines and in compliance with GLP (MacKenzie KM. 1986).

MCPA was administered at dose levels of 0, 50, 150 and 450 ppm (equivalent to approx. 4, 12 and 40 mg/kg bw, respectively). Two litters per generation were examined. The subsequent generation was reared with 25 male and 25 female rats of the second litter per dose. Gross-pathological and histopathological examinations were carried out and organs were weighed in the adults of the F0 and F1 generations and in the pups of the F1 and F2 generations.

At 450 ppm there was a significant reduction of body weight from weaning through the premating period in the F1b adults of both sexes. Body weights and weight gain were marginally reduced in F1a and F1b and significantly reduced in the F2a and F2b pups.

No substance-related effects on reproduction parameters were observed at any dose level. Gross-pathological or histopathological examinations did not indicate signs of compound-induced morphological actions in the offspring.

No information could be obtained in relation to sperm count or any evidence for decreased spermatogenesis as only a short summary was available for assessment.

RAC conclusions (MacKenzie KM. 1986): No effects on fertility and reproductive tissues were observed even at top dose level of 450 ppm (equivalent to approx. 40 mg/kg bw). RAC considers the highest dose of 450 ppm ~ 40 mg/kg bw/d to be rather low.

A one-generation study has been conducted for MCPA (Milburn, 2004), using Alpk:APfSD (Wistar-derived) rats (12/sex/group) and fed diets containing MCPA at concentrations of 0, 450, 750 or 1000 ppm. From day 1 post partum, the MCPA in the diet was reduced to 300, 500 or 667 ppm

to avoid particularly high doses being given to the lactating dams and pups. Litters were reared to weaning (day 29 post partum). Ten F1 pups/sex/group were then retained for a further 2 weeks of exposure to the original dietary concentrations of 450, 750 or 1000 ppm. Reproductive performance was determined from the outcome of mating, the duration of gestation and precoital interval. Pup viability and growth were monitored. Parental rats and offspring were necropsied and kidney, liver and ovaries/testes were weighed.

There were no treatment-related effects on reproduction or litter parameters. At 1000 ppm, absolute body weight was lower than controls during the premating exposure period. At 750 and 450 ppm, the difference in absolute body weight was significant only within the first 3 weeks pre-mating. Pup body weights were significantly lower only at 667 ppm and on day 29 of lactation.

No information could be obtained in relation to sperm count or any evidence for decreased spermatogenesis as only a short summery was available for assessment.

RAC concluded that (Milburn, 2004) there was no treatment-related effect on reproduction or litter parameters.

In the 90 day rat study (Shirakawa, 1973) decreased spermiogenesis was reported at 8.2 mg/kg bw/day. In the sub-acute neurotoxicity study (Mellert et al, 1994b), lower testes weights were recorded at 34 mg/kg bw/day and above and at the top dose of 177 mg/kg bw/day there was severe to extreme atrophy of the testes with oligozoospermia and aspermia. No effects on sperm were reported in the Kirsch et al, 1985 rat study, or in the interim kill at 52 weeks in the Maita, 1988 carcinogenicity study.

Additional studies were submitted during the CLH process. A publication by Sadlonova I et al. 2006, reported that a study was performed to investigate the toxicity of MCPA after repeated treatment according to OECD 409 with daily doses of 0, 1, 5 or 15 mg/kg bw/d during 90 days shows the relative weights of both testes were decreased in the males from the high dose group associated with focal testicular atrophy and loss of spermatogenic cells in the lobuli of testes.

Effects on development

Rats: 3 studies of developmental/teratogen toxicity with additional dose finding studies have been conducted in the rat (Tauchi, 1984 with MCPA –thioethyl, Hellwig & Hildebrand, 1992,3 with MCPA and Irvine 1980a with MCPA and Yasuda et al. 1982 with MCPEE)

In the (IIAR study) by *Tauchi 1984*, groups of 23 inseminated SPF Wistar Imamichi rats, were treated with MCPA-Thioethyl (approx. 93.3% pure) in daily doses of 0, 10, 40, 160 mg/kg body weight from the 6th to the 15th day of gestation.

Doses of test compound were suspended in distilled water containing 0.5% CMC-Na and given orally by stomach tube. At 160 mg/kg bw maternal toxicity was observed and the findings included reduced weight gain and food intake, increased water intake and increased spleen weight. At 160 mg/kg bw, foetuses showed reduced weight as well as retardation of ossification of sacral and caudal vertebra. No external, skeletal and visceral malformations were observed.

It was concluded that the substance is not teratogenic in rats, as the foetal effects were attributable to an unspecific consequence of maternal toxicity.

A range-finding study by *Hellwig et al, 1992* to investigate primarily maternal toxicity was carried out in Wistar rats. The range-finding study followed OECD 414 and was GLP compliant.

MCPA (94.22%) was administered to groups of ten pregnant females at dose levels of 0; 80; 120 ad 160 mg/kg bw once daily by gavage from day 6 through day 15 of gestation. The control

group received the vehicle only (0.5% CMC). The animals were observed daily throughout gestation for clinical signs of toxicity. On day 16 all dams were sacrificed, organs were weighed and macroscopically examined. The foetuses were delivered by Caesarean section, the weight of the foetuses and the placenta determined and an external examination was performed.

- Maternal toxicity was apparent at > 120 mg/kg bw, as indicated by reduced feed consumption and weight gain.
- Changes in clinical chemistry and increased enzyme activity, suggestive of anaemia and impaired liver function, occurred at > 80 mg/kg bw. Maternal increased kidney weight and decreased uterus weight at 160 mg/kg bw. Since termination was performed on day 16 p, c., the evaluation of the uterus content revealed limited information.
- Placental weights were reduced at > 120 mg/kg bw
- Foetal weights were reduced at all dose levels tested

Sufficient data were derived to allow choice of dose levels for the definitive study.

In the subsequent main study *Hellwig et al.1993,* the teratogenic potential and prenatal toxicity of MCPA (94.22%) was investigated at dose levels of 0, 15, 60 and 120 mg/kg bw/d following OECD 414 and in compliance with GLP.

Groups of 22 - 24 pregnant female Wistar rats received the test substance suspension once per day by gavage from day 6 through day 15 of gestation. The control group received the vehicle only (0.5% CMC). The animals were observed daily throughout gestation for clinical signs of toxicity and body weights were recorded throughout this period. On day 20 p.c. all surviving dams were sacrificed and the foetuses were delivered by Caesarean section and examined.

At 120 mg/kg bw/d, maternal body weight gain was approximately 23% lower than the control value for the dosing period, concomitant with significantly lower food consumption (up to 17% lower than the control value). There were no treatment-related macroscopic findings in the dams at necropsy. No maternal toxicity was associated with 15 or 60 mg/kg bw/d.

At 120 mg/kg bw/d, mean foetal body weight was approximately 12% lower than the control value. External examination revealed severe malformations of the head in two high-dose foetuses (brachygnathia, microglossia, unilateral anophthalmia, proboscis, aglosstomia, caudal displacement of the left ear, bilateral anophthalmia and hydrocephaly) believed to have arisen spontaneously. There was no overall treatment-related increase in the incidence of soft tissue or skeletal malformation. Reduced ossification of the foetal skull and sternebrae were observed and considered a possible association with reduced foetal body weight.

RAC concluded that the NOAEL for maternal and foetal toxicity is 60 mg/kg bw. There was no indication of a specific effect on the conceptus: in fact, the delayed foetal growth observed at top dose level was most likely an unspecific consequence of maternal toxicity.

The study by *Irvine, 1980*, non-GLP, dose levels of 0, 20, 50 and 125 mg/kg bw of MCPA in 1% MC were administered to Sprague-Dawley rats (five animals per level) by gavage from day 6 to day 15 of gestation. The animals were observed daily throughout gestation for clinical signs of toxicity and body weights as well as feed consumption were recorded. On day 21 p.c. all surviving dams were sacrificed and the foetuses were delivered and examined.

Neither substance-induced clinical signs of toxicity, impaired body weight gain in the dams nor findings in the foetuses were observed at any dose level.

No conclusion can be drawn, due to the low number of pregnant animals examined (five per group), resulting in an inadequate statistical power of the main study. Nevertheless, the overall

data from both the dose-finding and the main assays provide some reassurance that MCPA does not have a marked potential for eliciting teratogenic or embryotoxic effects.

The study by Yasuda, 1972, treatment with MCPEE resulted in a marked increase in foetal mortality at 2000 ppm, as shown by a significantly higher proportion of resorptions. Mean foetal weights were reduced in this group and, to a lesser extent, at 1000 ppm. The proportion of malformed foetuses was increased at 2000 ppm and (to a lesser extent) at 1000 ppm. At 2000 ppm, treatment resulted in an increase in the numbers of external malformations (primarily cleft palate) and visceral malformations (primarily ventricular septal defect); the incidence of ventricular septal defect was also increased at 1000 ppm. There was no data submitted related to the kinetic of MCPEE.

Conclusion: The NO(A)EL for maternal toxicity is 30 mg/kg bw/d based on reduced weight gain, bodyweight and food consumption at 60 mg/kg bw/d and above. The NOAEL for developmental toxicity is 30 mg/kg bw/d based on increased resportions, cleft palate, renal and cardiac malformations (ventricular septal defect). As no data was submitted in relation to the kinetic of MCPEE, this observation will not be considered in the overall WoE approach.

Rabbits: 5 studies on developmental/teratogen toxicity with additional dose finding studies have been conducted in the rabbit (Irvine 1978b and 1980, Hellwig et al 1992,-3, Ujhazy et al. 2006 with MCPA, Sugiya et al. 1985 and Sakamaki et al. 1985 with MCPA-thioethyl).

A range-finding study by *Irvine 1978b* in Dutch Belted rabbit, MCPA (purity not stated) was administered as 1.0% MC suspension at dose levels of 25 and 100 mg/kg bw by gavage to five animals each from day 1 to day 27 post insemination (p.i.); ten control animals received the solvent only. The dams were observed daily throughout gestation for clinical signs of toxicity and body weights were recorded throughout this period. On day 28 p.i. all does were sacrificed, subjected to macroscopic examination and the foetuses were delivered and examined.

Apparent maternal toxicity at 100 mg/kg bw with one compound-related death, ataxia and body weight loss and one rabbit died, while at 25 mg/kg bw no substance-induced toxicity was noted.

In all groups the pregnancy rate was low (6/10, 2/5 and 3/5 at 0; 25 or 100 mg/kg bw, respectively). At 100 mg/kg bw all foetuses died in utero; however, the prenatal mortality rate was approx. 50% also in the low dose group and the control group. No clear substance-related signs of embryo/foetotoxicity or teratogenicity was recorded for the foetuses. Foetal weights and lengths were slightly reduced at 25 mg/kg bw.

This poorly conducted study provided questionable indications to establish dosing levels for the main study.

In the main study by *Irvine 1980*, MCPA (purity not stated) as 1.0% MC suspension was administered to 15 - 18 female Dutch Belted rabbits at dose levels of 0, 5, 12; 30 and 75 mg/kg bw by gavage from day 6 to day 18 p.i. The control group consisted of 30 animals and received the carrier only. The animals were observed daily throughout gestation for clinical signs of toxicity and body weights as well as feed consumption were recorded. On day 28 p.i. all surviving does were sacrificed and subjected to gross pathology. The foetuses were delivered and examined.

Deaths from respiratory infection were observed at > 12 mg/kg bw. Although the deaths were not directly related to treatment, it is possible that the administration led to a higher susceptibility due to an impaired state of health.

At 75 mg/kg bw a loss in body weight was observed during the first half of treatment but at the end of pregnancy there was no difference in comparison to the control group.

An increased post implantation loss was observed at all dose levels.

No definitive conclusion can be drawn since a) at 75 mg/kg bw only the value was higher than that of the historical control data, however this was partly due to a dam having a whole litter resorbed; b) the post implantation loss was unusually low in the control group of this study in comparison to historical control data; c) there was no clear dose-response relationship considering the values of control; 5; 12 and 30 mg/kg bw groups.

Due to the increased mortality at > 12 mg/kg bw a maternal NOAEL could be tentatively put at 5 mg/kg bw. No definitive conclusion can be drawn as regards the NOAEL for prenatal toxicity.

A GLP range-finding study by *Hellwig et al 1992* to investigate primarily maternal toxicity was carried out in Russian rabbits. MCPA (94.22%) was administered to groups of five pregnant females at dose levels of 0, 50, 75 and 100 mg/kg bw once daily be gavage from day 7 through day 19 p.i. The control group received the vehicle only (0.5% CMC).

The animals were observed daily throughout gestation for clinical signs of toxicity. Body weight as well as feed consumption were recorded. Blood samples for haematology and clinical chemistry were taken on day 20 p.i. Subsequently all does were sacrificed, organs were weighed and macroscopically examined. The foetuses were delivered, the weight of the foetuses and the placenta were determined and an external examination was carried out.

Clear maternal toxicity was noted at > 75 mg/kg bw with deaths (2/5 and 1/5 at 100 and 75 mg/kg bw, respectively), reduced feed consumption and weight gain. No effect on the foetuses was observed at any dose level.

Sufficient data were derived for determining dose levels for the definitive study.

In the main GLP study Hellwig et al 1993. the prenatal toxicity of MCPA (94.22%) was investigated in Himalayan rabbits.

The test substance was administered to 13 - 14 females by gavage from day 7 to day 19 p.i. at dose levels of 0; 15; 30 and 60 mg/kg bw. The control group received the vehicle only (0.5% CMC). The animals were observed daily for clinical signs of toxicity, body weights were recorded several times during this period. On day 29 of gestation all surviving does were sacrificed, assessed by gross pathology and the foetuses were delivered by Caesarean section and examined.

At 60 mg/kg bw, severe maternal toxicity occurred: one death and one humane killing after abortion, weight loss and reduced feed consumption. At 30 mg/kg bw one doe with an affected general state aborted and was subsequently killed. No indication for embryo-foetotoxicity or teratogenicity at any dose level.

The NOAEL for maternal toxicity is 15 mg/kg bw and that for embryo- or foetal toxicity is at least 60 mg/kg bw.

In the *Sugiya et al 1985,* groups of 16 inseminated Japanese white rabbits received MCPA-Thioethyl (approx. 93.3% pure) in daily doses of 0, 40, 80, 160 mg/kg body weight from the 6th to the 18th day of gestation in (0.5% CMC-Na) solution and given orally by rubber stomach tube.

One maternal animal each in 80 mg/kg and 160 mg/kg groups showed anorexia followed by abortion and death. No effects on prenatal development were observed up to the top dose level.

The NOAEL for the dams was 40 mg/kg/day based on clinical signs, mortality, alteration of body weights and food intake, and abortions at 80 and 160 ppm; for the foetuses it was 160 mg/kg/day based on the lack of toxicity on the embryofoetal development.

In the *Sakamaki 1985*, Japanese white rabbits, 16 dams/dose group (0, 40, 80 and 160 mg/kg bw/d MCPA (IUCLID technical dossier) in 0.5% CMC) via oral gavage from gestation days 6-18. Foetuses examined for external, visceral and skeletal abnormalities. Termination day 29.

At 160 and 80 mg/kg bw/d, one female at each dose aborted. No other maternal effects, no developmental effects and no malformations were observed. At 40 mg/kg bw/day, no significant effects on dams or foetuses was noted.

The NOAEL for maternal toxicity is 40 mg/kg bw/d and the NOAEL for developmental toxicity was 160 mg/kg bw/d.

In the study by *Ujhazy et al. 2006* with MCPA in New Zealand White rabbits with dose 5, 10 and 25 mg/kg bw/d from day 6-27. The highest dose did not induce any signs of maternal toxicity. There was a significant decrease of foetal and placental weight compared with controls at 25 mg/kg/d. No other effects were reported

The NOAEL for maternal and developmental toxicity is 25 mg/kg bw/d. No clear effects of treatment observed.

Mice: 1 study on developmental toxicity have been conducted in the mice (Roll & Matthiasck 1983 with MCPA)

Groups of 13-34 mated female NMRI mice were dosed daily by gavage with 0, 50, 100, 200, 300, 400 or 500 mg/kg bw from day 6-15 of gestation. The pregnant females in the control group received peanut oil p.o. from the 6th to 15th day of pregnancy. At 500 mg/kg bw/d the maternal toxic range was reached, while up to 400 mg/kg bw/d no further toxic effects were observed or reported in the mothers, with the exception of reduced weight gain (in g) from day 0-18.

The dams showed a dose-dependent reduction in body weight gain already at 50 mg/kg bw/d at around 10% or above. However, it should be noted that the decreased body weight gain coincided with post implementation loss and decreased pup weight. Other signs of maternal toxicity such as clinical signs and mortality were reported with insufficient detail. An increase in post-implantation loss occurred at $\geq$ 300 mg/kg bw/day. Foetal body weight was reduced at $\geq$ 100 mg/kg bw/d in a dose-related pattern. An increased incidence of malformation including cleft palate and fused ribs was dose-related at $\geq$ 200 mg/kg bw/d.

Dose (mg/kg)	Number of females n	Embryos or foetuses n	Embryos or foetuses/ females n	Delivered embryos or foetuses		Resorptions			
						early		late	
				n	%	n	%	n	%
0	25	296	11.8	268	90.5	9	3.0	16	5.4
50	28	287	10.2	265	92.3	19	6.6	–	–
100	31	339	10.9	301	88.8	30	8.8	7	2.1
200	34	370	10.9	332	89.7	32	8.6	5	1.4
300	31	325	10.5	264	81.2*	50	15.4*	8	2.5
400	30	342	11.4	205	59.9**	122	35.7**	9	2.6
500	13	145	11.2	41	28.3**	96	66.2**	6	4.1

Dose (mg/kg)	Dead foetuses		Post-implantation loss (%)	Weight of the foetuses (g)	Cleft palate		Wavy ribs		Exencephalies		Microagnathias	
	n	% '			n	%	n	%	n	%	n	%
0	3	1.0	9.4	1.19	2	0.7	2	0.7	–	–	–	–
50	3	1.1	7.7	1.17	3	1.1	2	0.8	–	–	–	-
100	1	0.3	11.2	1.10*	6	2.0	2	0.7	–	–	–	–
200	1	0.3	10.3	0.95**	20	6.0*	12	3.6*	1	0.3	1	0.3
300	3	0.9	18.8*	0.82**	79	29.9**	23	8.7**	–	–	2	0.8
400	6	1.8	40.1**	0.71**	154	75.1**	38	18.5**	2	1.0	1	0.5
500	2	1.4	71.4**	0.58**	40	97.6**	3	7.3**	-	-	-	-
*P<0.009; **P<0.0027												

On account of the reduced foetal weights the NOAEL for embryo/foetotoxicity is 50 mg/kg bw/d. The NOAEL for maternal is not unequivolally clear. A decrease in weight gain in 10% or more is already present at 50 mg/kg bw/d. Important information on maternal toxicity such as clinical signs and mortality is insufficiently reported in the paper, but it is stated that there is no other effect than decreased weight gain except in the highest dose.

According to the authors the oral LD50 value for mice is 600 mg/kg bw/d; therefore, the selected higher dose levels were in the range of the cited LD50 value.

Consequently, it is possible that at clearly maternally toxic doses MCPA elicited unspecific teratogenic effects consisting mainly in cleft palates.

Conclusion on fertility

As reported in the repeated dose toxicity studies by Shirakawa 1973, Mellert et al 1994b and Sadlonova/Muckova 2005/6, effects on testes or spermiogenesis were observed. However, in the one generation and two generation studies no effects on fertility, reproductive tissue or in litter parameters was observed in these studies. **No classification for fertility is justified**.

The highest NOAEL of 88 mg/kg bw/d was determined from the one generation study of MCPA by Milburn 2004. In the MacKenzie,1986, the higest dose of 450 ppm ~40 mg/kg bw/d seems to be rather low. However, RAC did not have the original study report to assess the reliability of the whole study.

Conclusion developmental toxicity

Four studies have been conducted in the rat with additional two range-finding studies, while 5 studies have been conducted in the rabbit with additional two range-finding studies and one study in mice.

An overview of the studies:

Study		Findings
Rats		
MCPA	Irvine & Tucker (1978) [Range-finder: 0, 25, 100 mg/kg bw/d]	Maternal NOAEL: 100 mg/kg bw/d [No effects observed] Developmental NOAEL: 50 mg/kg bw/d [Reduced foetal size at 100 mg/kg bw/d]
	Irvine (1980) [0, 20, 50, 125 mg/kg bw/d]	Maternal NOAEL: 125 mg/kg bw/d [No effects observed] Developmental NOAEL: 125 mg/kg bw/d [No effects observed]
	Hellwig et al (1992) [Range-finder: 0, 80, 120, 160 mg/kg bw/d]	Maternal NOAEL: 80 mg/kg bw/d [Reduced food consumption & weight gain; haematology & clinical chemistry] Developmental NOAEL: 160 mg/kg bw/d [No effects observed]
	Hellwig & Hildebrand (1993) [0, 15, 60, 120 mg/kg bw/d]	Maternal NOAEL: 60 mg/kg bw/d [Reduced weight gain at 120 mg/kg bw/d] Developmental NOAEL: 60 mg/kg bw/d [Reduced foetal weight, skeletal ossification and severe malformations of the head in two foetuses at 120 mg/kg bw/d]
MCPEE	Yasuda & Maeda (1972) [~0, 2.7, 30, 60, 100 mg/kg bw/d]	Maternal NOAEL: 30 mg/kg bw/d [Reduced weight gain and food consumption at ≥60 mg/kg bw/d] Developmental NOAEL: 30 mg/kg bw/d [Increased resorptions; cleft palate, renal and cardiac malformations at ≥60 mg/kg bw/d]
MCPA-thioethyl	Tauchi (1984) [0, 10, 40, 160 mg/kg bw/d]	Maternal NOAEL: 40 mg/kg bw/d [Reduced weight gain and food consumption at 160 mg/kg bw/d] Developmental NOAEL: 40 mg/kg bw/d [Reduced foetal weight and skeletal ossification at 160 mg/kg bw/d]
Rabbit		
MCPA	Irvine & Tucker (1978) [Range-finder: 25, 100 mg/kg bw/d]	Maternal NOAEL: 25 mg/kg bw/d [mortality, clinical signs, weight loss at 100 mg/kg bw/d] Developmental NOAEL: 25 mg/kg bw/d [Foetal death at 100 mg/kg bw/d]
	Irvine (1980) [0, 5, 12, 30, 75 mg/kg bw/d]	Maternal NOAEL: 30 mg/kg bw/d [Reduced weight gain] Developmental NOAEL: 30 mg/kg bw/d [Implantation loss]
	Hellwig et al (1992) [Range-finder: 0, 50, 75, 100 mg/kg bw/d]	Maternal NOAEL: 50 mg/kg bw/d [Mortality, signs of toxicity and bodyweight loss at 100 mg/kg bw/d] Developmental NOAEL: 100 mg/kg bw/d [No effects observed]
	Hellwig & Hildebrand (1993) [0, 15, 30, 60 mg/kg bw/d]	Maternal NOAEL: 15 mg/kg bw/d [Mortality, signs of toxicity, reduced bodyweight gain and food consumption at 60 mg/kg bw/d; signs of toxicity at 30 mg/kg bw/d] Developmental NOAEL: 60 mg/kg bw/d [No effects observed]
	Ujházy et al. (2006) [0, 54, 10, 25 mg/kg bw/d]	Maternal NOAEL: 25 mg/kg bw/d [No clear effects of treatment observed] Developmental NOAEL: 25 mg/kg bw/d [No clear effects of treatment observed]
MCPA-thioethyl	Sugiya et al. (1985) [0, 40, 80, 160 mg/kg bw/d]	Maternal NOAEL: 40 mg/kg bw/d [Clinical signs, mortality body weight, food intake, abortion] Developmental NOAEL: 160 mg/kg bw/d [No effects]
	Sakamaki (1985) [0, 40, 80, 160 mg/kg bw/d]	Maternal NOAEL: 40 mg/kg bw/d [Mortality, abortion] Developmental NOAEL: 160 mg/kg bw/d [No effects]

Mouse		
MCPA	Roll & Matthiaschk (1983) [0, 50, 100, 200, 300, 400, 500 mg/kg bw/d]	Maternal NOAEL: 200 mg/kg bw/d [Reduced weight gain at ≥300 mg/kg bw/d] Developmental NOAEL: 50 mg/kg bw/d [Teratogenicity (post implantation lost , cleft palate) at ≥200 mg/kg bw/d; reduced foetal weight at ≥100 mg/kg bw/d]

Reliable studies performed in various species do not provide any evidence of developmental toxicity for MCPA-thioethyl or for the read-across substance MCPA. While a small number of published studies report apparently marked developmental toxicity.

Clear significant effects on malformation and post implantation loss, as well as, decreased pup weight were seen in the mouse study by Roll and Mattiaschk 1983. The only reported maternal toxicity was a decrease in weight gain which could not explain the high incidence of the specific malformation as cleft palate.

However the quality of this publication by Roll and Mattiaschk 1983 on the evaluation of the developmental toxicity of MCPA in the mouse is poor. The suitability of the dosing regime and selected animal model is questionable. Excessive doses were administered with rates up to 500 mg/kg (higher dose levels are in range of the cited LD50 value) and any resulting effects of maternal toxicity are insufficiently reported. The guideline acceptable study (Milburn, 2004) uses dietary concentrations up to 1000 ppm (89 mg/kg bw/d) and (MacKenzie, 1986) 450 ppm (39.6 mg/kg bw/d).

The study by Yasuda et al. 1972 tested the ethylester of MCPA for teratogenic effects in Wistar rats. The top dose of about 100 mg/kg bw/d resulted in two types of malformations that might be highlighted: Ventricular septal defects with 9.4% incidence at 50 mg/kg/d and 18.6% in 100 mg/kg/d and cleft palates only at the top dose 100 mg/kg/d with 5.9% evidence. However, there is no kinetic data submitted in relation to assess whether MCPEE will be converted to MCPA and in what extent. Therefore, the data from Yasuda et al. 1972 have not be taken into consideration for classification.

NMRI mouse and the sensitivity to "unspecific" development of cleft palates and the degree of purity of MCPA.

The NMRI mouse seems to be extremely sensitive to embryotoxic effects, especially cleft palate caused by phenoxyacetic acids. A study from the same institute in Berlin by Neubert et al. 1973: "Embryotoxic effects in mice treated with 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin", examines the effects of other phenoxyacetic acid herbicides, as well as, whether the content of impurities such as dioxin may affect embryotoxicity. The results show that using high doses 150-300 mg/kg bw/d, a single dose of 2,4,5-trichlorophenoxyacetic acid can produce cleft palates in the NMRI mouse. A maximal teratogenic effect is seen when the drug is administered on day 12 or 13 of gestation. The dioxin impurity, 2,3,7,8-tetrachlorodibenzo-p-dioxin also produced cleft palate at doses exceeding 1 µg/kg bw/d at day 6-15 of gestation in the NMRI mice and also as a single dose (20-50 µg/kg bw) given between day 7-13.

There is no information regarding the purity of the substance in the studies by Roll et al. 1983. The MCPA Task Force note in their comments that impurities like 2,3,7,8-TCDD have an influence on the malformations observed, however the dioxin impurity 2,3,7,8-TCDD does not seen to likely formed during the manufacturing process of MCPA but other kind of dioxins could be formed.

The results of the regulatory studies with rats and rabbits do not justify classification for developmental toxicity. The two published studies discussed above, Roll et al.1983 and Yasuda et al.1972 describe developmental toxicity that in principle warrants classification. However, there are relevant reasons for a limited reliability of these studies. The unknown purity is a rather

essential reason for downgrading the relevance of the studies, as well as limited reporting. In addition, the stress related mechanism for eliciting cleft palate in mice is an additional aspect decreasing concern. The results of Roll et al 1983 are very striking but no evidence of similar toxicity was seen in any of the other studies, which casts doubt on the realiability of this study.

For these reasons, these publications are not sufficient to support a classification for develomnetal toxicity

The overall conclusion is that, based on the regulatory studies with rats and rabbits, **no classification for developmental toxicity is warranted.**

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

The DS proposed to classify MCPA-thioethyl as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410 (M-factor of 10 for both) based on a fish 96h LC_{50} of 0.046 mg/L, 21d *Daphnia* and 72h algal NOECs of 0.009 mg/L and lack of rapid degradation.

The substance contains an impurity (4-chloro-o-cresol, CAS no. 1570-64-5) with a harmonized classification of Aquatic Acute 1; H400 (M-factor not specified; see Supplemental Information), at concentrations up to 0.2 % w/w. However, this does not affect the classification of MCPA-thioethyl, which is based on data for the substance itself.

Degradation

The substance hydrolyses with a half-life at 20 °C of 21.8 – 26.5 days at pH 4, of 6.6 – 12.5 days at pH 7 and < 12 hours at pH 9. Several groups of unknown metabolites are formed depending on pH, but the major transformation product is MCPA (4-chloro-o-tolyloxyacetic acid, CAS no. 94-74-6). In one test, MCPA appeared hydrolytically stable at all three pH values tested, but in a second test, its half-life was estimated to be 43.4 days (pH 4) and 211 days (pH 7) at 20 °C . These values were calculated assuming that the substance adsorbed into the container wall (and desorbed in the rinsate) could participate in the hydrolysis process; a re-calculation based on the amounts in the test solution gave an estimated half-life of 345 days (pH 4) and 159 days (pH 7).

MCPA-thioethyl also undergoes aquatic photolysis with a photolytic half-life of 0.74 days under laboratory conditions at pH 4 and 23.8 °C, equivalent to 1.01 days at 40° N in the summer. MCPA is formed as a first step, which is further transformed under the influence of light to a number of substances including 4-chloro-o-cresol, although neither this nor MCPA exceeded 10% of applied radioactivity (AR) after 2.2 days (one unidentified substance exceeded 10% of AR). Similar results were obtained at pH 7.

A ready biodegradation test according to OECD TG 301B using domestic activated sludge (adaptation not specified) resulted in 53.6% degradation after 28 days (carbon dioxide evolution). The substance is therefore not readily biodegradable.

An aerobic surface water simulation test (OECD TG 309) at 20 °C yielded a half-life in water of 0.73 and 1.1 hours at initial concentrations of 10 and 100 µg/L, respectively. Total levels of mineralisation were very low, reaching a maximum of 3.5% AR by day 21 at the low dose. Sterile controls indicated that the degradation was mostly abiotic. MCPA was the major transformation product (concentration ≥ 84% AR up until the end of the 30d study), with 4-chloro-o-cresol

formed in minor amounts (reaching a maximum of 2.1% AR); numerous unidentified substances were observed though none accounted for > 3% AR at any one time point.

Similar results were obtained in two natural water/sediment systems over 97 days, with whole system half-lives in the range of 0.06 – 0.08 days at 20 °C. Transformation products included MCPA (with a whole system half-life of 19 – 25 days) and 4-chloro-o-cresol, but mineralisation was a major degradation process (reaching a maximum of 61% after 97 days in one system and 68% after 63 days in the other).

In summary, MCPA-thioethyl is not readily biodegradable, and although primary transformation occurs rapidly in the environment (with a half-life < 16 days at 20 °C), the major transformation products are classified for environmental hazards (e.g. MCPA has a harmonised classification on Annex VI as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410). MCPA-thioethyl is therefore not considered to be rapidly degradable.

Bioaccumulation

The octanol-water partition coefficient (log K_{OW}) is 4.35 at pH 7 and 20 °C. Whilst this meets the CLP criterion for a bioaccumulative substance (log K_{OW} > 4), it is highly likely that MCPA-thioethyl is very rapidly metabolised to MCPA in fish and aquatic organisms (based on evidence of mammalian metabolism and the environmental fate studies). MCPA has a log K_{OW} much lower than 3. The DS therefore concluded that MCPA-thioethyl does not have potential to bioaccumulate in aquatic organisms.

Aquatic toxicity

Aquatic toxicity data are available for all three trophic levels, and a summary of the relevant information is provided in the following table (the key endpoints used in hazard classification are highlighted in bold). All studies were performed under semi-static conditions with results expressed in terms of geometric mean measured concentrations, unless stated otherwise. The DS did not provide any explanation of why flow-through was not considered for a substance that is subject to rapid primary degradation.

Table: Summary of relevant information on aquatic toxicity

Method	Test organism	Endpoint	Toxicity values in mg/L	Reference
Short-term toxicity to fish				
OECD TG 203	*Oncorhynchus mykiss* (Rainbow Trout)	96h LC_{50}	**0.046**	Juckeland, 2014
OECD TG 204		21d LOEC (mortality)	0.4 (nominal)	Grunert, 1991a
Long-term toxicity to fish				
N.A.				
Short-term toxicity to aquatic invertebrates				
OECD TG 202	*Daphnia magna*	48h EC_{50}	0.131	Mantilacci, 2014a
Long-term toxicity to aquatic invertebrates				
OECD TG 211	*Daphnia magna*	21d NOEC (mortality and other effects)	**0.009** (nominal)	Grunert, 1991b
Toxicity to algae and aquatic macrophytes				
OECD TG 201 (static)	*Desmodesmus subspicatus*	72h E_rC_{50} 72h E_rC_{10} 72h NOEC	> 2.3 0.8 **0.009** (all nominal)	Grunert, 1991c
OECD TG 221	*Lemna minor*	7d E_rC_{50} 7d NOE_rC	> 2.3 (nominal) 0.051	Mantilacci, 2014b

N.A. – data not available

The substance is used in herbicide and plant growth regulator applications, so algae and aquatic plants would be expected to be most sensitive. Growth rate inhibition of 50% or more was not achieved in the algal or plant tests at concentrations up to the nominal solubility limit in water. In the algal test, both stimulation and inhibition of cell growth was observed, depending on the concentration. The NOEC was the concentration at which no effect was observed compared to controls. In the *Lemna* test, 7d E_yC_{50}s based on frond number and dry weight were in the range 1 – 2 mg/L. A static algal toxicity test according to OECD TG 201 was also performed on *Pseudokirchneriella subcapitata* using a 20% formulation of MCPA-thioethyl (no information is provided about co-formulants). The 72h E_rC_{50} was 1.38 mg/L and the 72h NOE_rC was 0.44 mg/L (both expressed in terms of nominal active substance).

RAC notes that tests with other aquatic macrophytes (e.g. *Myriophyllum*) might provide additional sensitive end points, and so such data should be considered for classification purposes if they become available in future.

Comments received during public consultation

Four MSCA provided public comments, and three agreed with the proposed declassification (the fourth did not express a view).

One MSCA suggested that the log K_{OW} value should be used alone as an indicator of bioaccumulation potential in the absence of an *in vivo* study, but the DS pointed out that additional information can be considered on a case-by-case basis. In this case, extensive evidence of rapid primary transformation/metabolism to a more hydrophilic substance is a relevant factor, and RAC agrees with the DS that the substance is unlikely to be bioaccumulative.

Another MSCA said that the algal study using a formulation is only supplementary information and should not be used to classify the substance itself, and the DS agreed. RAC considers that studies with simple formulations of an active substance in water may be useful for classification purposes. However, in this case no information has been provided about co-formulants and in addition it is a static test and the results are expressed in terms of nominal concentrations; this may under-estimate toxicity given the rapid abiotic transformation of MCPA-thioethyl. RAC therefore agrees that this study should not be taken into account.

The fourth MSCA pointed out that the prolonged acute fish test (OECD TG 204) should not be used as a chronic study, and so the surrogate approach should be considered for chronic classification using the acute fish endpoint; the DS agreed but did not present the result of the surrogate approach. RAC also agrees, and notes that there is an apparent discrepancy between the two fish studies (suggesting at least an order of magnitude lower sensitivity over the longer time period). This was not commented on by the DS, but is possibly due to the life stage tested (furthermore, the OECD TG 204 study was performed on a slightly less pure substance (93% compared to 99% w/w)).

In addition, this MSCA asked for further information about the validity of the long-term *Daphnia* study and the Grunert (1991c) algal study endpoints for *Desmodesmus subspicatus* (particularly in view of the use of nominal concentrations, and the combination of stimulation as well as inhibition in the algal test). The DS clarified that:

- Measured test concentrations in the long-term *Daphnia* study ranged from 83 to 89% of nominal after 72 hours during the first renewal period for the three middle concentrations. Since these were > 80% of nominal the results were all based on nominal test concentrations. The lowest concentration (nominal 0.009 mg/L) was below the detection limit (not stated) and the highest concentration was not measured as there was 100% mortality by 48 hours. RAC notes that, since the critical data point from this study is the 21d *Daphnia* NOEC, which occurred

at the lowest test concentration, the DS should have provided the limit of detection, and the NOEC should be considered to be < 0.009 mg/L.

- The pH of the algal test was in the range 8.3 – 9.3, and that whilst most validity criteria were met, only two control replicates were used (the OECD TG 201 recommends six) so comparison with the guideline criteria for coefficient of variation is not meaningful. Normally the relevant endpoint for classification purposes is growth inhibition but the DS suggested that growth stimulation should not be ignored. RAC agrees that a significant change compared to the control may be detrimental to the organism, and stimulation might have adverse consequences (e.g. in terms of energy and nutrient depletion, etc.). It is therefore a relevant end point for classification. Given the rapid abiotic primary transformation of MCPA-thioethyl to MCPA observed in environmental fate tests, RAC notes that data expressed in terms of nominal concentrations may under-estimate toxicity. The alkaline pH of the static algal test as well as light irradiation would suggest that the parent substance did not remain in the solutions for long. RAC therefore considers the NOEC to be below 0.009 mg/L. The DS did not provide any additional details about the aquatic toxicity of MCPA so the significance of this cannot be assessed.

Assessment and comparison with the classification criteria

Degradation

MCPA-thioethyl is not readily biodegradable, and undergoes rapid primary transformation in the environment to classified substances. It is therefore not rapidly degradable according to the CLP Regulation.

Bioaccumulation

The substance is not potentially bioaccumulative, although it has a log K_{OW} value above the CLP Regulation threshold of 4, it is likely to be rapidly metabolised in fish to MCPA (a more hydrophilic substance with a log K_{OW} below 3).

Aquatic toxicity

Short-term aquatic toxicity data are available for three trophic levels. The lowest acute toxicity value is a 96h LC_{50} of 0.046 mg/L in fish. The substance therefore meets the criteria for classification with Aquatic Acute 1; H400. As 0.01 < L(E)C_{50} ≤ 0.1 mg/L, the M-factor is 10.

Reliable long-term aquatic toxicity data are available for invertebrates and aquatic plants (algae and *Lemna*), with relevant NOEC values below 0.009 mg/L (unbounded) in both cases. The substance therefore meets the criteria for classification with Aquatic Chronic 1; H410. As 0.001 < NOEC ≤ 0.01 mg/L, and the substance is not rapidly degradable, the M-factor is 10. No long-term data are available for fish, but based on the surrogate approach, considering the fish 96h LC_{50} of 0.046 mg/L the same classification and M-factor would apply, i.e. Chronic 1; H410 with an M-factor of 10.

RAC also notes that the same conclusion (Chronic 1; H410, M = 10) would be drawn even if the chronic *Daphnia* study would not be considered valid (see MSCA comment above). In this case, in the surrogate approach both fish and *Daphnia*'s acute toxicity (0.046 and 0.131 mg/L, respectively) should be considered.

Overall, RAC supports the DS' proposal and agrees to classify MCPA-thioethyl as **Aquatic Chronic 1; H410** and **Aquatic Chronic 1; H410** with an M-factor of 10 for both acute and chronic.

Additional references

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ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).

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