CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: MCPA-Thioethyl

EC Number: **246-831-4**

CAS Number: **25319-90-8**

Index Number: **Not allocated**

Contact details for dossier submitter: biuro@chemikalia.gov.pl

Bureau for Chemical Substances

30/34 Dowborczykow Street

90-019 Lodz, Poland

biuro@chemikalia.gov.pl

Version number: 1 **Date: 27.04.2016** **Updated 10 October 2016**

CONTENTS

PART A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	MCPA-thioethyl (phenothiol) (ISO)
EC number:	246-831-4
CAS number:	25319-90-8
Annex VI Index number:	Not included
Degree of purity:	Current agreed purity is 92% w/w. (Previous RMS Italy is considering equivalence from new source and an increase in min purity to 95.5%. Conclusion due 4Q'16)
Impurities:	No relevant impurities

1.2 Harmonised classification and labelling proposal

The current and proposed classification of both MCPA-thioethyl and MCPA are included in this section as, in relation to systemic toxicity, read across is proposed to data on MCPA-acid (rationale given under Section 4).

Table 2a: The current Annex VI entry and the proposed harmonised classification for MCPA-thioethyl

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Not included
Current proposal for consideration by RAC	Acute Tox. 4 H302 Aquatic Acute 1 H400 (M-factor 10) Aquatic Chronic 1 H410 (M-factor 10)
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 4 H302 Aquatic Acute 1 H400 (M-factor 10) Aquatic Chronic 1 H410 (M-factor 10)

Table 2b: The current Annex VI entry and the proposed harmonised classification for MCPA (CAS 94-74-6)

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Acute Tox. 4 H302 Skin Irrit. 2 H315 Eye Dam. 1 H318 Aquatic Acute 1 H400 Aquatic Chronic 1 H410
Current proposal for consideration by the applicant (MCPA Task Force) in the renewal dossier submitted under Reg. 1107/2009 and Regulation (EU) 844/2012	Acute Tox. 4 H302 Eye Dam. 1 H318 Aquatic Acute 1 H400 (M-factor 1) Aquatic Chronic 3 H412
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	To be decided.

1.3 Proposed harmonised classification and labelling based on CLP Regulation criteria

Table 3: Proposed classification according to the CLP Regulation for MCPA-thioethyl

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.2.	Flammable gases	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.3.	Flammable aerosols	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.4.	Oxidising gases	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.5.	Gases under pressure	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.6.	Flammable liquids	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.7.	Flammable solids	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.8.	Self-reactive substances and mixtures	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.9.	Pyrophoric liquids	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.10.	Pyrophoric solids	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.11.	Self-heating substances and mixtures	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.12.	Substances and mixtures which in contact with water emit flammable gases	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.13.	Oxidising liquids	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.14.	Oxidising solids	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
2.15.	Organic peroxides	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.

2.16.	Substance and mixtures corrosive to metals	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.1.	Acute toxicity - oral	**Acute Tox. 4 H302**	Not applicable	Not relevant	Not applicable
3.1.	Acute toxicity - dermal	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.1.	Acute toxicity - inhalation	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.2.	Skin corrosion / irritation	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.3.	Serious eye damage / eye irritation	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.4.	Respiratory sensitisation	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.4.	Skin sensitisation	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.5.	Germ cell mutagenicity	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.6.	Carcinogenicity	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.7.	Reproductive toxicity	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.8.	Specific target organ toxicity –single exposure	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.9.	Specific target organ toxicity – repeated exposure	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
3.10.	Aspiration hazard	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.
4.1.	Hazardous to the aquatic environment	**Aquatic Acute 1 H400** **Aquatic Chronic 1 H410**	M=10 (Acute) M=10 (Chronic)	Not relevant	Not applicable
5.1.	Hazardous to the ozone layer	Not classified	Not applicable	Not relevant	Conclusive but not sufficient for classification.

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Pictograms: GHS07, GHS09
Signal word: Warning
Hazard statements:
H302: Harmful if swallowed
H410: Very toxic to aquatic life with long lasting effects*

*Article 27 of CLP states that if a substance or mixture is classified within several hazard classes or differentiations of a hazard class, all hazard statements resulting from the classification shall appear on the label, unless there is evident duplication or redundancy. In accordance with Article 27 the following principles of precedence for hazard statements may apply to labelling:
- if the hazard statement H410 'Very toxic to aquatic life with long lasting effects' is assigned, the statement H400 'Very toxic to aquatic life' may be omitted.

Precautionary statements:
No precautionary statements are proposed since precautionary statements are not included in Annex VI of Regulation EC no. 1272/2008.

Proposed notes assigned to an entry:

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Not relevant for MCPA-thioethyl. There is no previous classification and labelling and no entry under Annex VI of the CLP Regulation.

As MCPA-thioethyl is rapidly metabolised to MCPA, the human health assessment of systemic toxicity endpoints relies on read-across to MCPA data (see Section 4 for justification).

MCPA is classified with the current Annex VI entry given above under Sections 1.2 Table 2b and in Section 2.3.1.

2.2 Short summary of the scientific justification for the CLH proposal

MCPA-thioethyl does not warrant classification for any physio-chemical hazardous properties.

The acute oral LD_{50} to rats was 450 mg/kg bw, meeting the criteria for classification under CLP as Acute Tox 4: H302. No classification is warranted for acute toxicity via the dermal or inhalation routes with the dermal LD_{50} being >5000 mg/kg bw and the inhalation LC_{50} >5 mg/L.

MCPA-thioethyl is not corrosive and does not warrant classification as a skin or eye irritant. No signs of irritation were observed in a rabbit skin irritation study and, in rabbit eye studies, observed effects were neither severe nor persistent enough to warrant classification according to the CLP criteria.

MCPA-thioethyl is not a dermal sensitiser (MCPA-thioethyl was negative in a maximisation test for dermal sensitisation) and therefore does not warrant classification for this endpoint.

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

In short-term studies, treatment–related effects were seen in a variety of tissues (spleen, haematological system, kidney, nervous system, testes, liver and gastrointestinal tract) in rats and dogs. The effects seen were considered either not to indicate a significant toxicological effect or were observed at doses above guidance values for classification. Therefore, no classification for STOT RE is considered warranted.

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.

Toxicokinetic studies examining the fate of MCPA-thioethyl following oral administration showed that even at 5 minutes post dosing, no MCPA-thioethyl was found, it having been converted to MCPA which was detected in whole blood and tissues before being eliminated, unchanged, in urine. Consequently, consideration is given to the effects of direct exposure to MCPA-thioethyl together with studies investigating exposure to the proximate metabolite, MCPA, which are relevant for the assessment of systemic toxicity resulting from exposure to MCPA-thioethyl. Further justification for this read across for systemic toxicity is provided in under Section 4.

There was no evidence of a carcinogenic effect for either MCPA-thioethyl or for MCPA in well conducted rat and mice studies, therefore no classification for carcinogenicity is warranted.

Neither MCPA-thioethyl nor MCPA was found to induce any adverse effect on fertility, reproduction, pregnancy outcome or littering in the rat. Three studies have been conducted and include one, two and three generation reproduction studies. Neither MCPA-thioethyl nor MCPA induced foetal malformation in rats or rabbits. In the rat, the developmental effects of reduced foetal body weight and reduced skeletal ossification were observed only in the presence of maternal toxicity. In the rabbit, no developmental effects were observed at maternally toxic doses. MCPA-thioethyl does not meet the criteria for classification as a reproductive toxicant.

There was no evidence in the available studies that MCPA-thioethyl has neurotoxicity or immunotoxicity potential.

In the aquatic environment, MCPA-thioethyl dissipates very quickly from the water layer (DT90 <1 day), degrading to MCPA by biotic and abiotic routes, followed by transfer of MCPA to sediment and mineralisation. One further metabolite: 2M4CP was identified as ‘significant’, but level in the whole water sediment system declined after 21 days.

MCPA-thioethyl degrades rapidly by photolysis with a DT50 equivalent to summer sunlight at 40°N of 1.69 days; to a number of minor (<10% AR) degradates. In hydrolysis studies, it is classified as ‘fairly hydrolysing’ with DT50s of 26.5 days and 7.4 days at pH 4 and 7 respectively.

Despite evidence of biotic degradation in an aerobic mineralisation study, the test for ready biodegradability for MCPA-thioethyl indicated that it does not meet the criteria to be considered as ‘Readily biodegradable’.

MCPA-thioethyl warrants classification as Aquatic Acute 1: H400: Very toxic to aquatic life with an M-factor of 10 on the basis that, for the most sensitive species, the 96 LC_{50} for trout (*Oncorhynchus mykiss*) is 0.046 mg/L. In relation to chronic exposure, classification as Aquatic Chronic 1: H410: ‘Very toxic to aquatic life with long lasting effects’ is warranted.

The **acute M factor of 10** will be applied, due to 96 hours **LC_{50}** of **0.046 mg a.i./L** obtained for the fish (*Oncorhynchus mykiss*).

MCPA-thioethyl is not rapidly degradable.

The **chronic M factor of 10** will be applied due to 21 days NOEC of 0.009 mg a.i./L obtained for *Daphnia magna* and 72 hour algal NOEC of 0.009 mg a.i./L obtained for freshwater alga species *Scenedesmus subspicatus.*

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

MCPA-thioethyl:

There is no current harmonised classification and labelling for MCPA-thioethyl.

MCPA:

The current classification of MCPA (proposed for read across for systemic toxicity, as justified under Section 4) is:

Signal word:	Danger	
Pictograms:	GHS05	
	GHS07	
	GHS09	
Hazard Statements:	Acute Tox. 4	H302
	Skin Irrit. 2	H315
	Eye Dam. 1	H318
	Aquatic Acute 1	H400
	Aquatic Chronic 1	H410

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

No longer relevant

2.4 Current self-classification and labelling

Current self-classification of MCPA-thioethyl is as follows:

Signal word:	Warning	
Pictograms:	GHS07	
	GHS09	
Hazard Statements:	Acute Tox. 4	H302
	Aquatic Acute 1	H400 (M-factor 10)
	Aquatic Chronic 1	H410 (M-factor 10)

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

According to Article 36 (2) CLP Regulation this point is not required for active substances in biocides and pesticides.

PART B.

SCIENTIFIC EVALUATION OF THE DATA

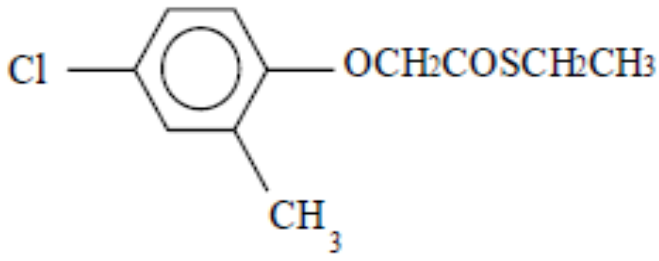
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC name:	MCPA-thioethyl (ISO)
EC number	246-831-4
CAS number:	25319-90-8
CAS name:	S-ethyl(4-chloro-2-methylphenoxy)ethanethioate
IUPAC name:	S-ethyl 4-chloro-o-tolyloxythioacetate
CLP Annex VI Index number:	Not allocated
Molecular formula:	$C_{11}H_{13}ClO_2S$
Molecular weight range:	244.7

Structural formula:



1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
MCPA-thioethyl	Current agreed minimum purity is 92.0: w/w.		Previous RMS Italy is considering equivalence from new source and an increase in min purity to 95.5%. Conclusion due 4Q'16.

Current Annex VI entry: No current entry

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
4-chloro-o-cresol (CAS 1570-64-5) (Also named 2M4CP in study reports cited in this document, and PCOC in literature references.)	≤0.2 % w/w	0.12-0.18% w/w	Annex VI Harmonised CLP is given below.

Current Annex VI entry:

Signal word: Danger

Pictograms: GHS05

GHS06

GHS09

Hazard Statements:		
	Skin Corr. 1A	H314
	Acute Tox. 3	H331
	Aquatic Acute 1	H400

Specific Concentration limits: STOT SE 3; H335: C ≥ 1%

The impurities have been taken into consideration in the classification of this substance. The relevant classifications for skin irritation/corrosion, STOT-SE, inhalation toxicity and acute aquatic toxicity have been derived from MCPA-thioethyl study data with typical concentrations 4-chloro-o-cresol and therefore any contribution to toxicity is accounted for.

Considering the endpoints triggering classification together with the fact that this impurity is present at <0.2% w/w, following the CLP Regulation relating to specific and/or generic concentration limits and the relevant cut off values, there is no contribution from 4-chloro-o-cresol to toxicity of the technical material influencing classification.

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
Not relevant				

Current Annex VI entry: No current entry

1.2.1 Composition of test material

The purity of the MCPA-thioethyl tested in the studies in this dossier ranged from 92 to 100%. Information on the actual purity used in each study, where known, is included in the IUCLID summaries (where provided). The test material in all cases is considered to be equivalent to and representative of, that specified above.

1.3 Physico-chemical properties

Table 8: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance	MCPA purified (100%): White, crystalline solid	Honda H., 1998	
Melting/freezing point	Melting point: 41.5°C (Purity: IUCLID technical dossier)	Honda H., 1998	
Boiling point	Not determinable. Purity = 100 %	Honda H., 1998	
Relative density	D_4^{22}= 1.29 (Purity: IUCLID technical dossier)	Honda H., 1998	
Vapour pressure	p(50°C) = 21.8 x 10^{-2} ±0.951 Pa p(40°C) = 7.31 x 10^{-2} ±0.383 Pa p(25°C) = 1.30 x 10^{-2} ±0.063 Pa (Purity: IUCLID technical dossier)	Nagayoshi E, 1999	
Partition coefficient n-octanol/water	logPow = 4.36 at pH 5 and 20°C logPow = 4.35 at pH 7 and 20°C logPow = 4.35 at pH 9 and 20°C (Purity: IUCLID technical dossier)	Hitchens J. & Frake E., 2014	
Water solubility	Solution Solubility at 20°C g/L 2.7x10^{-3} g/L at pH 4 and 20.5 ± 0.5°C	Brekelmans MJC., 2003	

Property	Value	Reference	Comment (e.g. measured or estimated)
	$2.5x10^{-3}$ g/L at pH 7 and 20.1 ± 1.0°C $2.4x10^{-3}$ g/L at pH 10 and 20.3 ± 0.5°C (Purity: IUCLID technical dossier)		
Solvent solubility	n-Hexane: 369 g/L Methanol: 144 g/L Xylene: >1000 g/L Dichloromethane: >1000 g/L Acetone: >1000 g/L Ethyl Acetate: >1000 g/L	Nagayoshi E, 1999	Values determined at 25°C
Surface tension	The surface tension of MCPA-thioethyl (as manufactured) is 60.93±0.87 mN/m at 20°C. The surface tension of purified (Purity: IUCLID technical dossier) MCPA-thioethyl is 70.3 mN/m (SD 0.2 mN/m) at 25±0.5°C.	D'Olimpio P., 2000 Mori V., 2015	Measured using a saturated aqueous solution. Measured at 90% of saturation solubility in water.
Autoflammability, self-ignition temperature	MCPA-thioethyl is not autoflammable	Flack I., 1996	
Flammability	MCPA-thioethyl is not flammable The test flame was held in position for 2 minutes during which time Phenothiol melted to a light brown liquid, without igniting.	Flack I., 1996	Measured – A.10 method (Oxidising properties (solids))
Explosive properties	MCPA-thioethyl does not possess explosive properties A Koenen test apparatus was used for the determination of heat, a fall hammer for the determination of sensitivity to shock and a friction test apparatus for determination of sensitivity to friction. Mechanical sensitivity There was no observable or audible reaction with mechanical sensitivity, shock and friction tests. Thermal sensitivity (effect of flame) There was no explosion or deformation with any of the test tubes, although the test substance did ignite.	Flack I., 1996	Measured – A.14 method (Explosive properties)

Property	Value	Reference	Comment (e.g. measured or estimated)
Oxidising properties	MCPA-thioethyl does not possess oxidising properties under the conditions of the tests. The fastest burning 60% barium nitrate/cellulose mixture from the extended test produced a maximum burning rate 2.60 mm/s. The fastest burning test substance/cellulose mixture from the extended test contained 70% test substance and had a burning rate of 1.37 mm/s. The test substance/cellulose mixtures burned slower than the barium nitrate/cellulose mixtures and therefore MCPA-thioethyl technical is considered not to be oxidising.	Flack I., 1996	Measured – A.17 method (Oxidising properties (solids))
Dissociation constant	Not determinable (Purity: IUCLID technical dossier)	Honda H., 1998	
Granulometry	Not relevant for CLP		
Viscosity	Study not required		Compound is a solid.

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for classification and labelling.

2.2 Identified uses

MCPA-thioethyl is approved for use in plant protection products in the EU, under the umbrella of the approval for MCPA and including its salts, esters and conjugates (Regulation (EU) No.540/2011; Regulation (EU) No. 762/2013; Directive 05/57/EC).

MCPA is used as an herbicide, but MCPA-thioethyl has authorisations for both herbicide and plant growth regulator applications.

When used as a plant growth regulator, MCPA-thioethyl improves the quality of fruit by increasing fruit size and preventing early fruit drop.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 9: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
Refer to Table 8 above.			

3.1.1 Physico-chemical hazards

3.1.2 Summary and discussion of physico-chemical properties

Refer to Table 8 above.

3.1.3 Comparison with criteria

In a standard flammability study MCPA-thioethyl was found to be not highly flammable. Experience in handling and use indicates it is not pyrophoric and does not react with water to liberate flammable gases. Further, it was tested in a standard self-ignition temperature study and no spontaneous ignition was observed.

MCPA-thioethyl was tested in a standard explosivity study where it was found to be not explosive under the influence of a flame and was not sensitive to impact or friction.

MCPA-thioethyl was tested in a standard oxidation study and was not oxidising.

3.1.4 Conclusions on classification and labelling

There is no classification warranted for physico-chemical properties.

4 HUMAN HEALTH HAZARD ASSESSMENT

Bridging statement for read across between MCPA-thioethyl and MCPA for systemic toxicity

In order to reduce unnecessary testing, particularly for toxicity testing on vertebrates, and in accordance with ECHA Guidance (Chapter R.6) and the Read-Across Assessment Framework (Reference: ECHA-15-R-07-EN), substances whose physicochemical and/or toxicological and/or ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity, may be considered as a group or “category” of substances. The similarities may be due to a number of factors

- Common functional group
- Common precursor or breakdown products
- Constant pattern in changing potency
- Common constituents or chemical classes

In the case of MCPA-thioethyl and MCPA, both having a common functional group (MCPA moiety), the read-across hypothesis is based on biotransformation to common compound(s) i.e. that MCPA-thioethyl is rapidly metabolised to MCPA (see 4.1 below). Indeed in a recent study (Johnson, 2012), 5 minutes post dose, no systemic exposure to MCPA-thioethyl was observed with only MCPA detected in whole blood and tissue extracts.

Comparison of the toxicological profile of MCPA-thioethyl and MCPA

A number of the MCPA-thioethyl toxicity studies were conducted before the formal introduction of GLP and/or the adoption of internationally recognised regulatory testing guidelines, whilst generally; the toxicity database for MCPA is more recent.

It is concluded that using the read-across approach with MCPA allows for the consideration of endpoint information and to adequately assign appropriate classification criteria for the systemic toxicology endpoints for MCPA-thioethyl. Where acceptable toxicity studies on MCPA-thioethyl, the results from these studies take precedence over those on MCPA. This approach is consistent with the conclusions of the DAR Addendum Vol 3 B5 (August 2002) which concluded that, since MCPA-thioethyl (as the thioester of MCPA) when administered to rat is rapidly and almost completely metabolised to MCPA, "*Although not acceptable for the today standards, the results and the NOELs of the other long term studies are in agreement with the data obtained with MCPA., it is conceivable to use the NOELs derived from long term studies of MCPA*." This position was finalised by the Standing Committee on the Food Chain and Animal Health (SANCO/4062/2001-final; 11 July 2008).

The toxicology properties and key endpoints for the two substances are tabulated below - Table 10. This illustrates that there are no key differences between the toxicological profiles of MCPA-thioethyl and MCPA.

Table 10: Comparison of systemic toxicity endpoints for MCPA-thioethyl and MCPA (source: List of Endpoints cited from SANCO/4062/2001-final; 11 July 2008)

Endpoint	**MCPA-thioethyl**	**MCPA**
Rate and extent of absorption	Rapidly absorbed > 96% in 168 hrs Cmax at 6 hours in rats.	Rapidly absorbed 75 % in 6 h, 40% in 12 h; Tmax 2 -2.4 h in rats; 58 % in 120 h (5mg/kg) in dogs; Tmax 4.54 h. 55 % in 96 h (15 µg/kg/bw) in humans; Tmax 1 h.
Distribution	Uniformly distributed	Uniformly distributed
Potential for accumulation	No potential for accumulation	No potential for accumulation
Rate and extent of excretion	168 hours post administration <1% dose remained[a] Primarily MCPA, in urine	Rapidly excreted: in rats, 90 % in 48 h, mainly in urine; in dogs, 58 % (5mg/kg) 34% (100 mg/kg) in 120 h, in urine; in humans, 51,5% at 5 mg/kg in 48 h, in urine.
Toxicologically significant compounds	MCPA	MCPA

Endpoint	MCPA-thioethyl	MCPA
Acute toxicity		
Rat LD_{50} oral	450 mg/kg b.w.	962 mg/kg b.w., female
Rat LD_{50} dermal	5000 mg/kg b.w.	> 4000 mg/kg b.w.
Rat LC_{50} inhalation	> 5.384 mg/L aerosol	> 6.36 mg/l 4h (head-nose; dust aerosol)
Short term toxicity		
Target / critical effect	Kidney/blood	Kidney/blood
Lowest relevant oral NOAEL / NOEL	2.2 mg/kg bw/d (90 d study in rats)	4.2 mg/kg bw/d (90 d study in rats)
Genotoxicity		
In vitro studies	No mutagenic potential	No relevant genotoxic potential
In vivo studies in somatic cells	No mutagenic potential	No relevant genotoxic potential
In vivo studies in germ cells	Not required	Not required
Long term toxicity and carcinogenicity		
Target/critical effect	Kidney, growth reduction	Kidney/blood
Lowest relevant NOAEL / NOEL	NOEL = 0.95 mg/kg bw/d; rat, 2 years	NOEL = 1.25 mg/kg bw/d; rat, 2 years
Carcinogenicity	No carcinogenic potential	No carcinogenic potential
Reproductive toxicity		
Reproduction target / critical effect	Reduced body weight gain in adults	Reduced body weight gain of pups at parentally toxic doses
Lowest relevant reproductive NOAEL / NOEL	500 ppm (approx. 25 mg/kg bw/d; rat 2-generation study)	150 ppm (8 mg/kg bw/d; rat 2-generation study)
Developmental target / critical effect	Maternal toxicity	Maternal toxicity
Lowest relevant developmental NOAEL / NOEL	40 mg/kg bw/d (rat and rabbit maternal toxicity)	15 mg/kg bw/d (rabbit maternal toxicity)
Neurotoxicity / Delayed neurotoxicity		
Acute neurotoxicity	No neurotoxicity	No neurotoxicity
Subchronic neurotoxicity	No neurotoxicity	No neurotoxicity

a '> 75% of radioactivity was recovered in all animals by 24 hours post dose

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Following a single oral administration of [^{14}C] MCPA-thioethyl to male rats, > 96% of the dosed radioactivity was recovered over 168 hours. (Johnson, 2012). Excretion of radioactivity was rapid (> 75% of radioactivity was recovered in all animals by 24 hours post dose). At 168 hours post administration, < 1% dose was retained in the carcasses, indicating that recovery of radioactivity was essentially complete at that time. Radioactivity was excreted predominantly in the urine, with only ca 1 – 2% dose excreted via the faeces.

The distribution of radioactivity was investigated in male rats by Whole-Body Autoradiography following a single oral administration of [^{14}C] MCPA-thioethyl at a target dose level of 25 mg/kg. (Johnson, 2012). Distribution of radioactivity was rapid, with radioactivity concentrations quantifiable in most tissues at 0.08 hours after dosing (the first sacrifice time). Greater radioactivity concentrations were present in the stomach wall, kidney cortex, kidney outer and inner medulla, small intestine wall, liver, pancreas, urinary bladder wall, cardiac blood and spleen. These were the only tissues containing radioactivity concentrations greater than whole blood, and the concentrations in the majority of tissues were appreciably less than in whole blood. The lower radioactivity concentrations were associated with the testes, whole-eye, spinal cord, seminal vesicles, brain, and bone surface.

The pattern and distribution of radioactivity remained similar throughout the time periods investigated. Despite the wide distribution of radioactivity at 0.08 hours, concentrations in the vast majority of tissues subsequently increased and continued to do so until 3 hours following dose administration when C_{max} in the majority of tissues was reached. By 6 hours after dosing radioactivity concentrations in the majority of tissues had declined significantly (to approximately 50% of those achieved at C_{max}). Radioactivity concentrations continued to decline until 12 hours post dose (the last time period investigated). However, radioactivity concentrations in almost all tissues were still quantifiable, with only the spinal cord and the seminal vesicles below the limit of quantification at this time.

Tissue: whole blood radioactivity concentration ratios were generally less than unity, with the exception of the stomach wall, kidney cortex, kidney outer medulla, liver, cardiac blood, pancreas and spleen. Tissue: whole blood radioactivity concentration ratios in the kidney inner medulla were generally greater than unity, except at C_{max}.

Selected tissue samples were harvested for metabolite profiling at 5 minutes and 3 hours post dose administration. HPLC analysis showed that even at the first sampling time point (5 minutes post dose), no systemic exposure to MCPA-thioethyl was observed with only MCPA detected in whole blood and tissue extracts. In addition, selected pooled urine and faeces samples were also analysed by HPLC. An additional peak, only detected during the analysis of pooled urine samples, was identified by mass spectrometry as a possible hydroxylated metabolite of MCPA and the predominant metabolite was likewise confirmed by mass spectrometry as MCPA (and a glycine conjugate of MCPA). Metabolites within the faeces extracts were unable to be identified using the supplied method, however, no single component represented >1% administered dose.

Following a single intravenous dose of [^{14}C] MCPA-thioethyl (1 mg/kg) to male rats, the highest whole-blood concentrations of radioactivity (5.55 µg equivalents MCPA-thioethyl/mL) were observed 5 minutes after dosing, the first time of sampling. (McDonald, 2014). The extrapolated whole-blood concentration at time zero (C_0) was 5.76 µg equivalents MCPA-thioethyl/mL and the terminal half-life was 2.6 hours. Whole blood radioactivity concentrations were still measurable at

the final sampling time (24 hours). Chromatographic analysis showed, even at the first sampling time (5 min post-dose), no evidence for intact parent MCPA-thioethyl in whole blood extracts, with only a component which corresponded chromatographically to MCPA detected in whole blood extracts, suggesting that, in the male rat, there was no systemic exposure to MCPA-thioethyl.

4.1.2 Human information

Human volunteers given an MCPA dose of 0.015 mg/kg bw/day exhibited a peak plasma concentration after 1 hour (Kolmodin-Hedman et al., 1983). In a comparison review of these metabolism studies in rats, dogs and humans, Timchalk (2004) showed that dogs had a longer plasma half-life than rats and humans. At a dosage of 5 mg/kg bw, the plasma half-life was 63 hours in dogs, which was considerably higher than that in rats (6 hours) or humans (11 hours), although humans received a lower dose of MCPA (0.015 mg/kg bw).

4.1.3 Summary and discussion on toxicokinetics

MCPA-thioethyl is rapidly absorbed following ingestion and converted to MCPA. MCPA in turn, is not extensively metabolized and is eliminated primarily in the urine, mostly as unchanged MCPA, in rats, dogs and humans. However, dogs have a longer plasma half-life and slower elimination than other species, including humans. In a comparison review of metabolism studies in rats, dogs and humans, Timchalk (2004) showed that dogs had a longer plasma half-life and slower elimination than rats and humans, which resulted in a substantially higher body burden of MCPA, at comparable doses, than in other species. In previous studies with organic acids with similar pharmacokinetic properties, the dog had a more limited capacity than other species to excrete organic acids via the kidney. The authors suggested that the following two mechanisms may be responsible for this decrease in renal clearance: saturation of renal secretion and increased renal tubule reabsorption. These differences in the pharmacokinetics of MCPA and other related organic acids between dogs and other species suggest that the use of dog toxicity data for determining human health risk may not be appropriate.

4.2 Acute toxicity

Table 11: Summary table of relevant acute toxicity studies

<table>
<tr><th>Method</th><th>Results and Remarks</th><th>Reference</th></tr>
<tr><td>Rat (Wistar)
Oral: gavage
5/sex/group
OECD Guideline 401
GLP
Test material: MCPA-thioethyl tech. (Purity: IUCLID technical dossier)
Single oral dose of 300, 400, 500 or 600 mg/kg bw in aqueous suspension
Observed for 14 days</td><td>In all treatment doses, tremor, sedation, ataxia, convulsions, snow shoving, increased salivation and mortalities were seen. No significant macroscopic histology findings.
Mortalities
<table>
<tr><td>mg/kg bw</td><td>300</td><td>400</td><td>500</td><td>600</td></tr>
<tr><td>Males</td><td>0/5</td><td>1/5</td><td>4/5</td><td>5/5</td></tr>
<tr><td>Females</td><td>0/5</td><td>0/5</td><td>4/5</td><td>5/5</td></tr>
</table>
The oral LD_{50} in Wistar rats was calculated to be 450 mg/kg bw for both sexes.</td><td>Dickhaus 1991a
M-CA 5.2.1*</td></tr>
</table>

<table>
<tr><th>Method</th><th>Results and Remarks</th><th>Reference</th></tr>
<tr><td>Rat (Sprague-Dawley)
Oral: gavage
10/sex/group
No guideline stated: similar to OECD 401 but only 7 days observations.
Conducted pre-GLP
Purity of test substance (phenothiol) not stated
Single oral dose of 455 (males only), 592, 769, 1000 and 1300 mg/kg bw in peanut oil.
Observed for 7 days</td><td>Depression, closing of eyelids, lacrimation, ataxia were seen 30 minutes after dosing, followed by loss of reflex, extension of limbs and rough hair which continued for one day. Hypothermia, coma, polyuria and hypersensitivity were also observed after one day. Most of the rats tested were dead after 2 days.
Mortalities
<table>
<tr><td>mg/kg bw</td><td>455</td><td>592</td><td>769</td><td>1000</td><td>1300</td></tr>
<tr><td>Male</td><td>0/10</td><td>1/10</td><td>5/10</td><td>7/10</td><td>10/10</td></tr>
<tr><td>Female</td><td>-</td><td>0/10</td><td>7/10</td><td>9/10</td><td>10/10</td></tr>
</table>
The oral LD_{50} in SD rats was calculated to be 790 mg/kg bw in males and 877 mg/kg bw in females.</td><td>Itoh and Toida 1974</td></tr>
<tr><td>Mouse (CFI)
Oral: gavage
5/sex/group
OECD Guideline 401
GLP
Test material: MCPA-thioethyl tech. (Purity: IUCLID technical dossier)
Single oral dose of 400, 500, 640 or 800 mg/kg bw in aqueous suspension
Observed for 14 days</td><td>Signs of toxicity included tremor, pinched eyes, increased eye secretion, sedation, ataxia, tonic-clonic convulsions, snow shoving and increased salivation. Most of the animals in both highest dosage groups died within 24 hours. No remarkable macroscopic findings.
Mortalities
<table>
<tr><td>mg/kg bw</td><td>400</td><td>500</td><td>640</td><td>800</td></tr>
<tr><td>Males</td><td>0/5</td><td>1/5</td><td>4/5</td><td>5/5</td></tr>
<tr><td>Females</td><td>0/5</td><td>0/5</td><td>4/5</td><td>5/5</td></tr>
</table>
The oral LD_{50} in CFI mice was calculated to be 580 mg/kg bw for both sexes.</td><td>Dickhaus, 1991b
M-CA 5.2.1</td></tr>
<tr><td>Mouse (ICR)
Oral: gavage
10/sex/group
No guideline stated: similar to OECD 401 but only 7 days observations
Conducted pre-GLP
Purity of test substance (phenothiol) not stated)
Single oral dose of 455 (males only), 592, 769, 1000 and 1300 mg/kg bw in peanut oil.
Observed for 7 days</td><td>Depression, stretch of tail and paralytic staggering gait were observed one hour after dosing. Later, extension of limbs in body sag, closing of eyelids and loss of righting reflex were also observed and continued for one day. Muscle relaxation especially in paw, rigid tonus by touch stimulus and lateral position were also noted in some mice. Hypothermia, lacrimation, light cyanosis and clonic seizures were seen after one day. Most of the mice tested were dead after 2 days; deaths of females were later than males
Mortalities
<table>
<tr><td>mg/kg bw</td><td>455</td><td>592</td><td>769</td><td>1000</td><td>1300</td></tr>
<tr><td>Male</td><td>0/10</td><td>1/10</td><td>5/10</td><td>8/10</td><td>10/10</td></tr>
<tr><td>Female</td><td>-</td><td>0/10</td><td>4/10</td><td>6/10</td><td>10/10</td></tr>
</table>
The oral LD_{50} in ICR mice was calculated to be 811 mg/kg bw in males and 749 mg/kg bw in females.</td><td>Itoh and Toida 1974</td></tr>
</table>

Method	Results and Remarks	Reference
Rat (Sprague-Dawley) Inhalation (4 h, whole body exposure) 5/sex/group Guideline - not stated but similar to OECD 403. GLP Test Material – MCPA-thoioethyl (Purity: IUCLID technical dossier) Single 4 h whole body exposure to dust of 0.44 µg/L . Observed for 14 days.	No mortalities or signs of toxicity were recorded. It was concluded that MCPA-thioethyl has a LC_{50} > 0.044 mg/L air.	Church, 1984
Rat (Wistar) Inhalation (4 h nose only exposure) 5/sex/group OECD 403 guideline GLP Test Material: Technical MCPA-thioethyl (Purity: IUCLID technical dossier) Single 4 h nose only exposure to 5.384 mg/L air	Slight bradypnea (slow breathing) during exposures and animals were moderately subdued 1 h after exposure but recovered thereafter. Body weight gain was reduced for the first 4 days, but recovered by day 8. No mortalities. The LC_{50} of MCPA-thioethyl is > 5mg/L air.	Mulier, 2003*
Rat (Wistar) Dermal 5/sex/group OECD Guideline 402 GLP Test material: MCPA-thioethyl tech. (Purity: IUCLID technical dossier) 5000 mg/kg bw, semi-occlusive dressing Observed for 14 days	There were no mortalities and no signs of toxicity or local effects. The dermal LD_{50} in male and female Wistar rats was > 5,000 mg/kg bw	Dickhaus, 1991c* M-CA 5.2.2
Rat (Sprague Dawley) Dermal 12 male and 6 female//group Guideline- not stated but similar to OECD 402 Not GLP Test material: MCPA-thioethyl tech. (Purity: IUCLID technical dossier) 5000 mg/kg bw, semi-occlusive dressing Observed for 14 days	There were no mortalities and no signs of toxicity or local effects. The dermal LD_{50} in male and female Sprague Dawley rats was > 5,000 mg/kg bw	Kobayashi, 1983 M-CA 5.2.2

* Key studies for consideration of MCPA-thioethyl classification

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Rat

Groups of 5 male and female Wistar rats were dosed with 300, 400, 500 or 600 mg/kg bw MCPA-thioethyl in an aqueous suspension. Animals displayed symptoms as tremor, sedation, ataxia, convulsions, "snow shoving", increased salivation and mortalities. At autopsy, there were no significant macroscopic signs. The oral LD_{50} in Wistar rats for MCPA-thioethyl was calculated to be 450 mg/kg bw for both sexes. (Dickhaus 1991a).

In a non-GLP study, groups of 10 Sprague-Dawley rats were administered by gavage doses up to 1300 mg/kg bw MCPA-thioethyl dissolved in peanut oil as 10% solution. Animals showed signs of depression, closing of eyelids, lacrimation and ataxia 30 minutes after dosing, followed by loss of reflex, extension of limbs and rough hair which continued for one day. Hypothermia, coma, polyuria and hypersensitivity were also observed after one day. Most of the rats tested were dead after 2 days. The onset of symptoms and death appeared more slowly in female rats than in males. Under the conditions of this study the oral LD_{50} was calculated to be 790 mg/kg bw in males and 877 mg/kg bw in females (combined LD_{50} 833 mg/kg bw). (Itoh and Toida, 1974).

Mouse

Groups of 5 male and female CF1 mice were dosed with 400, 500, 640 or 800 mg/kg bw MCPA-thioethyl in an aqueous suspension. Animals displayed tremor, pinched eyes, increased eye secretion, sedation, ataxia, tonic-clonic convulsions, "snow shoving" and increased salivation. Most of the animals in the two highest dosage groups died within first 24 hours. At autopsy, there were no significant macroscopic findings. The oral LD_{50} in CF1 mice for MCPA-thioethyl was calculated to be 580 mg/kg bw for both sexes. (Dickhaus, 1991b).

In a non-GLP study, groups of 10 ICR strain mice per sex were gavage dosed with MCPA-thioethyl in peanut oil as 10% solution up to 1300 mg/kg bw. Signs of depression, stretch of tail and paralytic staggering gait were observed one hour after dosing. Later, extension of limbs in body sag, closing of eyelids and loss of righting reflex were also observed and continued for one day. Muscle relaxation especially in paw, rigid tonus by touch stimulus and lateral position were also noted in some mice. Hypothermia, lacrimation, light cyanosis and clonic seizures were seen after one day. Most of the mice tested were dead after 2 days and deaths of female were later than male. Under the conditions of this study the oral LD_{50} in ICR mice for MCPA-thioethyl was calculated to be 811 mg/kg bw in males and 749 mg/kg bw in females (combined LD_{50} is 780 mg/kg bw for both sexes). (Itoh and Toida, 1974).

4.2.1.2 Acute toxicity: inhalation

Groups of 5 male and 5 female Sprague Dawley (SD) rats were exposed, whole body, to a dust aerosol of MCPA-thioethyl at a concentration of 0.44 µg/L for 4 hours. No mortalities or signs of toxicity were observed. Rats gained body weight and at autopsy there were no macroscopically treatment related effects. Under the condition of this study, it was concluded that MCPA-thioethyl is of low acute inhalation toxicity in SD rats, the LC_{50} > 0.044 mg/L air. (Church, 1984)

Mulier, 2003, investigated the acute inhalation toxicity of MCPA-thioethyl in Wistar rats. Five Wistar rats of each sex were exposed nose only to a nominal 5 mg/L MCPA-thioethyl and observed for 15 days. There were no mortalities; animals showed bradypnea during the exposure period and were

subdued for the first hour after exposures. There were no significant macroscopic findings at necropsy. The 4 h inhalation LC_{50} of MCPA-thioethyl is > 5mg/L air (dust).

4.2.1.3 Acute toxicity: dermal

MCPA-thioethyl was applied to the backs of 5 male and 5 female Wistar rats at a dose of 5000 mg/kg bw. There were no mortalities or signs of local or systemic toxicity. The acute dermal toxicity is therefore > 5000 mg/kg bw. (Dickhaus, 1991c).

In a non-GLP study, MCPA-thioethyl was applied to the shorn backs of 12 male and 6 female Sprague Dawley rats at a dose of 5000 mg/kg bw. There were no mortalities or signs of systemic toxicity. The acute dermal toxicity is therefore > 5000 mg/kg bw. (Kobayashi,1983).

4.2.1.4 Acute toxicity: other routes

No information on other routes.

4.2.2 Human information

A major manufacturer of MCPA-thioethyl has surveyed its manufacturing workforce every 6 months according to the Japanese Ordinance on Industry Safety and Health Article 44 and 45. After 20 years of periodical control, no significant adverse effects have been noted in workers involved in the production plant and, specifically, there have been no reports of sensitisation/allergenicity in plant workers or applicators. No cases of poisoning were reported since the start of production in 1971 through to 2002. (Kondo, 2002).

Workers involved in the current manufacture of MCPA-thioethyl and other active substances are tested periodically in a range of seven different monitoring tests (including blood analysis for various parameters) as required by Italian Legislation. In 30 years of testing there has been no incidence of significant modification in these tests. There have been no case or reported sensitization / allergenicity to chemical compounds in plant workers or applicators. (Taino, 2015).

The lowest published lethal oral dose for MCPA in humans is 814 mg/kg bw.. Symptoms of acute exposure to large doses of MCPA have been reported as a result of poisoning from accidental ingestion and accidental exposure during manufacturing or application in the field. The symptoms include fatigue, weakness, anoxia, nausea, vomiting, diarrhoea, lowering of the blood pressure, body temperature disturbance, progressive hypotension, ataxia, neuromuscular irritability and convulsion (Health Canada, 2010; Guidelines for Canada Drinking Water Quality).

4.2.3 Summary and discussion of acute toxicity

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.

4.2.4 Comparison with criteria

With a rat oral LD_{50} of 450 mg/kg bw (i.e. Acute Toxicity Estimate (ATE) >300 but ≤ 2000 mg/kg bw), MCPA-thioethyl warrants classification as Acute Tox. 4; H302 according to CLP. The associated Acute Toxicity point Estimate (ATE) for MCPA-thioethyl is 450 mg/kg bw.

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

4.2.5 Conclusions on classification and labelling

CLP: Acute Tox. 4: H302

300 < ATE ≤ 2000 mg/kg bw (Acute Toxicity point Estimate (ATE): 450 mg/kg bw).

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

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 (see Section 4.12.1.1.; Mellert et al, 1994a).

No signs of systemic toxicity were evident after 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 bi-yearly 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.

4.3.2 Comparison with criteria

Substances that have produced significant non-lethal toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant non-lethal toxicity in humans following single exposure, are classified as STOT-SE 1 or 2. Classification is supported by evidence associating single exposure to the substance with a constant and identifiable effect.

Classification in STOT-SE 3 is reserved for transient target organ effects and is limited to substances that have narcotic effects or cause respiratory tract irritation.

There was no evidence for specific target organ toxicity following single exposures to MCPA-thioethyl via the oral, dermal or inhalation routes.

4.3.3 Conclusions on classification and labelling

CLP: No classification

4.4 Irritation

Irritation data are provided as supportive information only.

4.4.1 Skin irritation

Table 12: Summary table of relevant skin irritation studies

Method	Results and Remarks	Reference
Rabbit (New Zealand White) 5 adults OECD Guideline 404 GLP Test Material: MCPA-thioethyl (Purity: IUCLID technical dossier) 0.5g in distilled water under semi-occlusive dressing Observed for 4 days	No skin reactions or signs of systemic toxicity were recorded. Primary Irritation Index was 0. MCPA-thioethyl was not a skin irritant under the conditions of this study	Dickhaus 1991 d M-CA 5.2.4*
Rabbit (Japanese Albino) 3/sex/group Guideline not stated; similar to OECD 404 Evaluated according to Draize Not GLP Test Material: MCPA-thioethyl (Purity: IUCLID technical dossier) 0.5g applied under an occlusive dressing Observed for 7 days	Slight erythema (1 on a scale of 4) was observed on intact and abraded skin in one male animal but had recovered by 48 h. Skin irritation index was 0.08 (maximum possible score 8). No systemic effects were observed. MCPA-thioethyl was practically non-irritating to the rabbit skin	Kobayashi, 1982

* Key studies for consideration of MCPA-thioethyl classification

4.4.1.1 Non-human information

MCPA-thioethyl was applied to the intact skin of 5 New Zealand White rabbits. No skin reactions were observed. MCPA-thioethyl was therefore not a skin irritant under the conditions of this study (Dickhaus, 1991d).

In a non-GLP study**,** MCPA-thioethyl was applied to six male and six female albino rabbits (Japanese White strain) for 24 hours under an occlusive dressing according to the method of Draize examining intact and abraded skin (Kobayashi, 1982). Slight, transient erythema was observed on intact and abraded skin in one of six animals, recovering to normal within 48 hours. The skin irritation index was 0.08 (maximum possible score 8). Neither systemic effects nor intoxication symptoms were observed. Under the conditions of this study, MCPA-thioethyl was considered to be practically non-irritating to the rabbit skin.

4.4.1.2 Human information

Data from 20 years of monitoring on a manufacturing plant did not show any adverse effects. (See Section 4.2.2).

4.4.1.3 Summary and discussion of skin irritation

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 does not irritate the skin of rabbits.

4.4.1.4 Comparison with criteria

The major criterion for classification under CLP of a substance as irritant to skin, is the mean value of the scores for either erythema/eschar or oedema calculated in at least 2 of 3 tested animals. Mean value of ≥ 2.3 to ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from grading at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions triggers classification. A substance may also be classified as an irritant if inflammation persists to the end of the observation period in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling.

No signs of erythema or oedema were observed (also no inflammation persists to the end of the observation period), therefore, MCPA-thioethyl does not meet the criteria for classification according to the CLP Regulation.

4.4.1.5 Conclusions on classification and labelling

CLP: No classification

4.4.2 Eye irritation

Table 13: Summary 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 Guideline 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 classified as non-irritant to rabbit eyes.</td><td>Dickhaus (1991e) M-CA 5.2.5*</td></tr>
<tr><td>Rabbit (Japanese White)
3 male and 3 female
Guideline not stated – similar to OECD 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 a slight irritant to rabbit eyes, but criteria for classification are not met.</td><td>Kobayashi, 1982</td></tr>
</table>

* Key studies for consideration of MCPA-thioethyl classification

4.4.2.1 Non-human information

MCPA-thioethyl was administered to the conjunctival sac of the eyes of six New Zealand white rabbits. The conjunctivae showed slightly increased redness accompanied by slight increased secretion up to 8 hours after application but there was full recovery by 24 hours. Under the conditions of this study, MCPA-thioethyl is not an eye irritant. (Dickhaus, 1991e).

In a non-GLP study (Kobayashi, 1982), slight conjunctival redness was observed in all animals at 24 h with slight discharge. All animals except for one female had fully recovered by 48 h, with the latter showing recovery by day 4. Under the conditions of this study, MCPA-thioethyl is a slight irritant to rabbit eyes.

4.4.2.2 Human information

Data from 20 years of monitoring on a manufacturing plant did not show any adverse effects. (See Section 4.2.2).

4.4.2.3 Summary and discussion of eye irritation

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.

4.4.2.4 Comparison with criteria

Under CLP, a substance should be classified as an eye irritant (Category 2) if, in at least 2 of 3 animals tested, a positive response is observed for corneal opacity ≥ 1 and/or iritis ≥ 1 and/or conjunctival redness ≥ 2 and/or conjunctival oedema ≥ 2; calculated as mean scores following grading at 24, 48 and 72- hours and which is fully reversible within 21 days. In the Dickhaus, 1991 study there were no corneal or iris effects and the mean score for conjunctival erythema and/ or chemosis was 0 at 24 hours.

In neither of these studies are the effects severe or persistent enough to warrant classification according to the CLP criteria.

4.4.2.5 Conclusions on classification and labelling

CLP: No classification

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

No data available.

4.4.3.2 Human information

Data from 20 years monitoring on a manufacturing plant did not show any adverse effects. (See Section 4.2.2).

4.4.3.3 Summary and discussion of respiratory tract irritation

There are no data to suggest that MCPA-thioethyl is a respiratory irritant.

4.4.3.4 Comparison with criteria

There are no data to suggest that MCPA-thioethyl is a respiratory irritant therefore, no classification is warranted.

4.4.3.5 Conclusions on classification and labelling

CLP: No classification

4.5 Corrosivity

4.5.1 Non-human information

Solution of MCPA-thioethyl does not have a pH ≤ 2 or ≥ 11. Data from rabbit skin and eye irritancy studies indicate that MCPA-thioethyl is not corrosive to animal tissue (see section 4.4 above).

4.5.2 Human information

Data from 20 years of monitoring on a manufacturing plant did not show any adverse effects (see Section 4.2.2).

4.5.3 Summary and discussion of corrosivity

No signs of corrosion were observed in the available irritation studies, therefore, MCPA-thioethyl is not considered to be corrosive.

4.5.4 Comparison with criteria

MCPA-thioethyl was not corrosive in the available irritations studies and does not have a pH of ≤2 or ≥ 11.5. Therefore, MCPA-thioethyl does not meet the criteria for classification in accordance with CLP.

4.5.5 Conclusions on classification and labelling

CLP: No classification

4.6 Sensitisation

4.6.1 Skin sensititsation

Table 14: Summary table of relevant skin sensitisation 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*

* Key studies for consideration of MCPA-thioethyl classification

4.6.1.1 Non-human information

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 (Sugiya, 1985).

4.6.1.2 Human information

Data from 20 years monitoring on a manufacturing plant did not show any signs of allergenicity. (See Section 4.2.2).

4.6.1.3 Summary and discussion of skin sensitisation

No signs of an allergic response were observed in the available dermal sensitisation study, therefore, MCPA-thioethyl is not considered to be a dermal sensitiser.

4.6.1.4 Comparison with criteria

Although the mouse Local Lymph Node Assay is now the study of choice for identification and classification of dermal sensitisers, a substance may be classified as a skin sensitiser on the basis of a positive test result in approved designated animal tests, including the Magnusson and Kligman guinea pig maximisation test. A substance can be categorised as a Sub-Category 1A skin sensitiser if

the response ≥ 30% at ≤ 0.1 % intradermal induction dose or as a Sub-Category 1B skin sensitiser if the response ≥ 30 % at > 1 % intradermal induction dose

MCPA-thioethyl was negative in a maximisation test and therefore does not meet the criteria for classification as a skin sensitiser.

4.6.1.5 Conclusions on classification and labelling

CLP: No classification

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

No information.

4.6.2.2 Human information

Data from 20 years monitoring on a manufacturing plant did not show any adverse effects. (See Section 4.2.2).

4.6.2.3 Summary and discussion of respiratory sensitisation

There are no data to suggest that MCPA-thioethyl is a respiratory sensitiser.

4.6.2.4 Comparison with criteria

There are no data to suggest that MCPA-thioethyl is a respiratory sensitiser therefore, no classification is warranted.

4.6.2.5 Conclusions on classification and labelling

CLP: No classification

4.7 Repeated dose toxicity

Table 15: Summary table of relevant repeated dose toxicity studies

Method	Results and Remarks	Reference
Studies in Rats		
90 day oral Rat; Wistar 15 rats/ sex/ group Test Material: MCPA. Purity (Purity: IUCLID technical dossier) Guideline: OECD 408	**450 ppm (37 mg/kg bw/day):** Increased creatinine in females and reduced cholesterol and calcium in males. Increased absolute and relative kidney weights in male. **150 ppm (12 mg/kg bw/day):** increased absolute and relative kidney weights. **50 ppm (4.1 mg/kg bw/day):** No adverse changes.	Kirsch et al 1985a*

GLP Dietary doses of 0, 50, 150 and 450 ppm equivalent to 0, 4.1, 12 and 37 mg/kg bw/day Histopathology on tissues from all animals.	**NOEL 4.1 mg/kg bw/day**	
90 day oral Rat; Sprague Dawley 15 rats/ sex/ group Test Material: MCPA-thioethyl. Purity not stated Guideline – not stated Not to GLP Dietary doses of 0, 1.4, 7, 35 and 150 mg/kg bw/day Tissues taken from 10/sex/group for histopathological examination.	**150 mg/kg bw/day:** Body weight gain and food consumption reduced with animals losing weight during weeks 11 to 13 becoming emaciated and uncoordinated. Statistically significant lower leukocyte and erythrocyte counts, haemoglobin concentration and haematocrit values; increased GPT and BUN concentration in females and lower blood glucose and higher serum GPT in males. Absolute organ weights generally lower than controls. Discoloration of kidneys and spleen. Increased haemosiderin pigment in spleen red pulp in all test animals and pigment in epithelial cell of kidney cortex tubules **35 mg/kg bw/day:** Discoloured kidneys. **NOEL 35 mg/kg bw/day**	Morrow et al, 1974a*
90 day oral Rat: Wistar 10 rats/ sex/ group Test Material: MCPA-thioethyl. (Purity: IUCLID technical dossier) Guideline – not stated Not to GLP Dietary doses of 0, 30, 100, 300 and 1000 ppm (equivalent to 0, 1.4, 8.2, 19 and 57 mg/kg bw/day)	No significant effects were seen on food intake, body weight, mean body weight gain, organ weight and organ/body weight ratio, hematological and biochemical findings **1000 ppm (57 mg/kg bw/day):** atrophy of the splenic lymphatic follicle (2/10). Decreased spermiogenesis (5/10). Atrophy of nerve cells in spine and brain stem in males and females. **300 ppm 19 mg/kg bw/day):** atrophy of the splenic lymphatic follicle was observed in females at 300 ppm (4/10). Decreased spermiogenesis (5/10). Lung sarcoma (3/10) males. Atrophy of nerve cells and brain stem was observed in 2/10 females **100 ppm (8.2 mg/kg bw/day):** decreased spermiogenesis (5/10). Atrophy of nerve cells in spine and brain stem in 1/10 female. **NOEL 1.4 mg/kg bw/day**	Shirakawa 1973*
Subacute neurotoxicity Rat: (Chbb:THOM (SPF) 15/sex/group Dietary for 90 days Guideline: not stated GLP: not stated Test Material: MCPA (Purity: IUCLID technical dossier) 0, 50, 500 or 2500 ppm (equivalent to 0, 3, 34 and 177 mg/kg bw/day for males and 0, 4, 42 and 188 mg/kg bw/day for females Functional observational battery and motor activity assessment on	**2500 ppm (177 mg/kg bw/day):** bodyweights decreased by 27 -21% for males and females, respectively and body weight gain reduced by 42 and 48%. Food consumption also significantly reduced. Decreased forelimb grip in males on day 50, decreased hind limb grip strength in females at day 85 and decreased landing foot splay on day 22. Motor activity was slightly reduced for both males and females on days 22, 50 and 85. Haematological changes in red cell parameters consistent with macrocytic anaemia. Reductions in white cell counts in females and reduced leucocyte count in females. Prolonged prothrombin times in females. Serum glucose, total protein and globulins and increased urea, creatinine and enzyme activity. Serum triglycerides significantly reduced for both sexes. Absolute liver weight increased for females.	Mellert et al, 1994b*

10 rats / sex/ group prior to dosing and during weeks 4, 8 and 13. Blood and urine taken at termination. Neurological tissues on 5/sex/group examined histo-pathologically.	Relative kidney weight significantly increased for males. Lower relative adrenal weights (females) and testes weights could not be attributed to the lower body weights. Pathology showed marked hepatocellular cytoplasmic eosinophilia and granular cytoplasm. Minimal to moderate foam cells in the lung of males and females. A number of animals showed hypercellularity of the bone marrow, consistent with impaired red cell production Increased lipid in adrenals. Diffuse atrophy of the testes (severe to extreme) in all males with oligozoospermia and aspermia in 3 and 7 rats, respectively. Thymic atrophy occurred in 3 females. No treatment-related neurohistopathology. **500 ppm (34 mg/kg bw/day):** bodyweight gain reduced by 12% at week 13. Serum triglycerides for males significantly reduced compared to controls. Relative kidney weight significantly increased for males, associated with increase urea and creatinine levels, but no pathology correlate. Lower relative adrenal weights (females) and testes weights could not be attributed to the lower body weights. Increased lipid in adrenals. **50 ppm (3 mg/kg bw/day):** No adverse effects. **NOAEL 50 ppm (3 mg/kg bw/day) based on reduced bodyweight gain in females, increased relative kidney weight in males and increased adrenal lipid at 500 ppm (34 mg/kg bw/day).**	
Rat: Fisher F34/DuCrj Carcinogenicity- chronic toxicity (24 months): Interim study data up to 12 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, 0.8, 7.7, and 78.7 mg/kg bw/day at week 52 for males. 10/sex group for haematology at 13 weeks. 10/sex/group for haematology, clinical chemistry and pathology at 26, 52.	**2000 ppm (78.7 mg/kg bw/day):** decreased body weight gain throughout the study up to week 52 accompanied by decreased food consumption. Haemolytic anaemia in both sexes at weeks 13, 26 and 52. Females had increase urinary output at weeks 26 and 52. Urinary protein was increased in males at week 26 and in females at week 52. High levels of GOT and ALP for males and females at weeks 26 and 52. Increased thyroid weight in both sexes at weeks 26 and 52. Males and females showed splenic congestion and dilatation of sinuses at 52 weeks and increased brown pigment deposition in the renal tubular cells at 52 weeks. **200 ppm (7.7 mg/kg bw/day):** males had slightly lower body weights (2-3%) during the first year associated with decreased food consumption. Increased thyroid weights for males only at week 52. **20 ppm (0.8 mg/kg bw/day):** no adverse effects **NOEL 20 ppm (equivalent to 0.8 mg/kg bw/day) after 52 weeks of treatment.**	Maita, 1988*
Rat: Wistar Carcinogenicity- chronic toxicity (24 months); data up to 52 weeks Guideline: OECD 453 GLP Test Material: MCPA	This study report and data are unavailable to this applicant and therefore data for assessment of effects up to 52 weeks cannot be evaluated. The main study results (taken from the DAR) are given in **Section 4.10 Carcinogenicity.**	Kirsch et al, 1988

(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 group 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 after 2 years administration Histopathology on all animals		
Studies in Mice		
90 day oral Mouse (Charles River, Albino) 15 mice/ sex/ group Test Material: MCPA-thioethyl. Purity not stated Guideline – not stated Not to GLP Dietary doses of 0, 1.4, 7, 35 and 150 mg/kg bw/day Tissues taken from 10/sex/group for histopathological examination Hematological, clinical blood chemistry and urine analyses were performed only on control and 150 (and occasionally on 35) mg/kg bw/day animals).	No abnormal behavioural reactions were noted among any of the treated animals. No significant differences were seen in haematological parameters investigated. **150 mg/kg bw/day:** Reduced bodyweight gain. At autopsy, discoloured livers. Increased splenic haemosiderin deposits. **NOEL 35 mg/kg bw/day**	Morrow et al, 1974b*
90 day oral Mouse: DDY strain 10 rats/ sex/ group Test Material: MCPA-thioethyl. (Purity: IUCLID technical dossier) Guideline – not stated Not to GLP Dietary doses of 0, 30, 100, 300 and 1000 ppm (equivalent to 0, 3.9, 13.1, 39, and 141 mg/kg bw/day for both sexes, combined) No urinalysis and limited clinical chemistry	No significant differences were noted for food intake, body weight, mean body weight gain, organ weight and organ/body weight ratios. **1000 ppm (150.3 mg/kg bw/day females):** Changes in cranial nerve system were observed in female mice **300 ppm (35.1 mg/kg bw/day in males, 42.6 mg/kg bw/day in females):** 6 mice died and were cannibalized. In both male and female there was a marked increase in GOT. **NOEL 42.6 mg/kg bw/day**	Shirakawa, 1973*
Mouse: ICR (Crj:CD1) Carcinogenicity- chronic toxicity (18 months). Effects up to 52 weeks. Guideline: OECD 451 GLP Test Material: MCPA-thioethyl. (Purity: IUCLID technical dossier) 70 male and 70 females/ group	**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. **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.	Harada, 1992*

0, 30, 300, 1500 ppm in diet, equivalent to 0, 2.8, 29.3, and 151 mg/kg bw/day 20/sex/ grp terminated at 52 weeks At 52 and 78 weeks, blood smears taken from 10/sex/group. Histopathology on all animals.	**NOEL for toxicity (based on limited parameters examined) was 30 ppm (equivalent to 2.8 mg/kg bw/day).**	
Mouse: B6C3F1 Carcinogenicity (24 months). Effects up to 52 weeks. 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 grp used for heamatology and interim sacrifice at week 52 Histopathology on all animals	This study report and data are unavailable to this applicant and therefore data for assessment of effects up to 52 weeks cannot be fully evaluated. The main study results (taken from the DAR) are given in **Section 4.10 Carcinogenicity.**	Kűhborth et al, 1988
Studies in Dogs		
90 day oral Beagle dog Dietary administration Test material: MCPA (Purity: IUCLID technical dossier); MCPA (Purity: IUCLID technical dossier) and pure MCPA (MCPA.P) 4/sex/group received 0, 3, 12 or 48 mg/kg be/day 4/sex/group received 0, 0.3, 1 or 12 mg/kg bw/day 4/sex/group received 12 mg/kg bw/day MCPA.P Guideline not stated Not conducted to GLP Ophthalmoscopy, haematological, clinical chemistry and urinalysis conducted during the study. Feacal blood, liver and kidney function tests were conducted. At autopsy, organs were weighed and tissues examined histologically.	**48 mg/kg bw/day:** One dog died and the remainder, bar one, were killed in a moribund state. Severe clinical symptoms included pustules, papules, necrotic skin lesions, focal stomatitis, conjunctivitis, diarrhoea, anorexia, dehydration, lethargy and signs of icterus. Food consumption was markedly reduced and weight loss occurred at this dose level. Increased creatinine and GPT activity. Glucose values were decreased. Bilirubin and OCT values were elevated and low albumin and protein values occurred in some dogs prior to death. The Na+ and K+ contents in the urine of dogs were lower than in controls. Bilirubin was detected in urine of some dogs. Kidney function was affected. Liver function was affected in the surviving dog of the high-dose group. Faecal blood was recorded in dogs. Relative kidney weights were increased. Gross pathological examination revealed jaundice, enlarged gall bladder, haemorrhages in the intestine, stomach, and lungs, pale livers, a tan-coloured liver and a swollen, yellow liver. Degenerative and/or regenerative changes were found in the liver, kidneys and gastro-intestinal tract. **12 mg/kg bw/day MCPA or MCPA.P:** Muco purulent conjunctivitis was seen in a few dogs. Body weight gain was decreased. Blood urea values were slightly increased in males and females. Increased creatinine and GPT activity. Kidney function was affected. Faecal blood was observed in 2 dogs fed MCPA.P. Prostate weights reduced in dogs fed MCPA. Enlarged gall bladders were found in two dogs fed MCPA. Dogs fed MCPA showed a slight increase in incidence and degree of infiltrates of mononuclear cells in the liver. Slight to moderate bile duct proliferation was seen in some dogs	Reuzel et al, 1980*

	fed MCPA or MCPA.P. Increased creatinine values, alanine aminotransferase activity and blood urea values **3 mg/kg bw/day:** Blood urea values were slightly increased in males and females. Increased creatinine and GPT activity. Kidney function was affected. **1 mg/kg bw/day:** no adverse effects **0.3 mg/kg bw/day:** no adverse effects **No difference in toxicity could be established between MCPA technical product and purified MCPA.** **NOEL 1 mg/kg bw/day for both sexes.**	
2-year oral Beagle dogs 4/ sex/ group Test Material: MCPA-thioethyl. Purity not stated Guideline – not stated Not to GLP Dose levels: 0, 20, 100 and 500 ppm in the diet	No unusual behavioural reactions were seen at any dose. **500 ppm (approximately 25 mg/kg bw/day)**: One animal was sacrificed after 14 weeks of treatment; prior to sacrifice the animal had a depressed erythrocyte count, haemoglobin, haematocrit as well as an elevated serum GPT value. Gross pathological examination revealed pale intestines and pale and oedematous lungs. Male body weights were reduced from 4th week (-10%) throughout the study with a maximum at 13-16th week (-20%). Erythrocyte count, haemoglobin, haematocrit was decreased in females between 3 and 12 months of treatment. Males showed a reduced haemoglobin concentration between months 3 and 12. Morphological changes in the liver and kidneys. The primary lesions in the liver were extramedullary hematopoiesis and were multifocal in distribution and graded minimal to moderate in severity. Pigments present in kidney convoluted tubules. **100 ppm (approximately 5 mg/kg bw/day):** morphological changes in the liver and kidneys. The primary lesions in the liver were extramedullary hematopoiesis. Pigments present in kidney convoluted tubules. The NOEL was tentatively considered to be 20 ppm, equivalent to approximately 1.0 mg/kg bw/day, based on the presence of pigments in liver and kidneys. There was insufficient data to consider a definitive NOEL as there was no statistical evaluation of some data **Tentative NOEL: approximately 1.0 mg/kg bw/day**	Mastalski, 1976*
Study in rabbits		
21day dermal Rabbit: New Zealand White 5/sex/ group Test Material: MCPA (Purity: IUCLID technical dossier) Guideline: OECD 410 GLP Dose levels 0, 10, 100 and 1000 mg/kg bw/day Applied moistened in water for 6 h/day for 21-22 days	No mortalities or treatment-related clinical signs were seen. No effects on body weight, food consumption, haematology, biochemistry, urinalysis and organ weights. **1000 mg/kg bw/day:** erythema and edema progressing from slight to well-defined were recorded in 5/10 animals by day 10. Additionally, discoloration, dryness and desquamation occurred in a varying incidence. Histopathologically minimal diffuse acanthosis with or without hyperkeratosis of the treated skin was recorded in all animals. **100 mg/kg bw/day:** slight erythema and edema in a	Baldrick P et al 1992*

Skin reactions scored following Draize Clinical chemistry, haematology and urinalysis prior to sacrifice. At autopsy, organs weighed and tissues examined histologically.	varying degree and intensity were noted and minimal diffuse acanthosis occurred also in some animals. **10 mg/kg bw/ day:** no skin reactions were noted. **NOEL for systemic toxicity 1000 mg/kg bw/day** **NOEL for dermal irritation 10 mg/kg bw/day.**	

* Key studies for consideration of MCPA-thioethyl classification

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Rat

The subchronic toxicity of MCPA was examined in 15 male and 15 female Wistar rats which received dosages of 0, 50, 150 or 450 ppm (corresponding approximately to 0, 4, 12 and 37 mg/kg bw/day) in the diet for 3-months.The study followed OECD 408 and was GLP compliant. Clinical chemistry and haematology parameters and urinalysis were carried out within the study period. At the end of treatment all animals were sacrificed, organs were weighed and histopathology was performed. Clinical chemistry at 450 ppm showed increased creatinine values in females as well as reduced cholesterol and calcium values in the males. Increases in absolute and relative kidney weights were observed in males at 150 ppm and above. No compound-related changes were noted at the lowest dose level. Thus, the NOEL was 50 ppm (approx. 4.1 mg/kg bw/day) (Kirsch, 1985).

In a non-GLP study, groups of 15 male and 15 female Sprague-Dawley albino rats were fed with 0, 1.4, 7, 35, 150 mg/kg bw/day technical MCPA-thioethyl for 3 months. Lower total body weight gains associated with lower food consumption was evident at 150 mg/kg bw/day. During weeks 11, 12, 13 these animals lost weight and became emaciated and uncoordinated. Statistically significant lower leukocyte count, erythrocyte count, haemoglobin concentration and haematocrit values and higher GPT and BUN concentration in females and lower fasted blood glucose and higher serum GPT were seen in males at 150 mg/kg bw/day. Absolute organ weights of high dose animals were generally lower than controls, accounted for, in part, by the lower weight gains of these animals. Discoloured kidneys were observed at 35 and 150 mg/kg/day in both sexes but this is considered of equivocal toxicological significance and was not observed in the chronic toxicity study. Spleens were discoloured at 150 mg/kg bw/day. The no observed-effect level is 35 mg/kg bw/day for males and females (Morrow, L. 1974).

In a further non-GLP study, groups of 10 male and 10 female Wistar albino rats were fed with 0, 30, 100, 300 and 1000 ppm (corresponding to 0, 1.4, 8.2, 19, and 57 mg/kg bw/day) of MCPA-thioethyl for 3 months. No marked differences between treated rats and controls were observed in terms of food intake, body weight, mean body weight gain, organ weight and organ/body weight ratio, hematological and biochemical findings. Atrophy of the splenic lymphatic follicle was observed in females at 300 ppm (4/10) and 1000 ppm (2/10). Decreased spermiogenesis was observed in male animals at 100 ppm and above. Lung sarcoma appeared at 100 ppm (1/10, male) and 300 ppm (3/10 male) but not at 1000 ppm or in any groups of treated females. Atrophy of nerve cells in the spine and brain stem was observed in both sexes at 1000 ppm, in 2/10 females at 300 ppm and in 1/10 female at 100 ppm. The no observed effect level was considered to be 30 ppm, corresponding to 1.4 mg/kg bw/day (Skirakawa, 1973).

In a subacute neurotoxicity study (Mellert et al, 1994b), groups of 15 Chbb:THOM rats/ sex/group were fed diets containing MCPA in the diet at 0, 50, 500 or 2500 ppm (equivalent to 0, 3, 34 and 177 mg/kg bw/day for males and 0, 4, 42 and 188 mg/kg bw/day for females). A functional observational battery and motor activity assessment was conducted on 10 rats / sex/ group prior to dosing and during weeks 4, 8 and 13. Blood and urine was taken at termination and neurological tissues from 5/sex/group were examined histopathologically. At 500 and 2500 ppm bodyweights were decreased and food consumption was significantly reduced at 2500 ppm. At 2500 ppm, there was decreased forelimb grip in males on day 50, decreased hind limb grip strength in females at day 85 and decreased landing foot splay on day 22. Motor activity was slightly reduced for both males and females on days 22, 50 and 85. Haematological changes in red cell parameters at 2500 ppm were consistent with macrocytic anaemia; there were also reductions in white cell counts in females, reduced leucocyte count in females and prolonged prothrombin times in females. At 2500 ppm, glucose, total protein and globulins and increased urea, creatinine and enzyme activity were evident and serum triglycerides were significantly reduced for both sexes. Serum triglycerides were also reduced for males at 500 ppm. Absolute liver weight was increased for females at 2500 ppm; relative kidney weights were significantly increased for males at 500 and 2500 ppm. Lower relative adrenal weights (females) and testes weights at 500 and 2500 ppm could not be attributed to the lower body weights. Pathology of animals at 2500 ppm showed marked hepatocellular cytoplasmic eosinophilia and granular cytoplasm. There was minimal to moderate foam cells in the lung of males and females. A number of animals at 2500 ppm showed hypercellularity of the bone marrow, consistent with impaired red cell production Increased lipid in adrenals was evident at 500 and 2500 ppm. Diffuse atrophy of the testes (severe to extreme) was seen in all males at 2500 ppm with oligozoospermia and aspermia in 3 and 7 rats, respectively. Thymic atrophy occurred in 3 females at 2500 ppm. There was no treatment-related neurohistopathology. The NOAEL was 50 ppm (3mg/kg bw/day).

In a long term toxicity/carcinogenicity study (Maita, 1988) Fisher F34/DuCrj rats were fed diets containing 0, 20, 200 and 2000 ppm MCPA-thioethyl (equivalent to 0. 0.8. 7.7 and 78.7 mg/kg bw/day after 52 weeks. Ten rats/sex/group were sacrificed at 26 and 52 weeks for haematology, clinical chemistry and histopathology. Decreased body weights were recorded at 200 and 2000 ppm over the 52 weeks, associated with decreased food consumption. Changes in haematology parameters at 2000 ppm at weeks 13, 26 and 52 were indicative of haemolytic anaemia. At 2000 ppm, females had increased urinary output at weeks 26 and 52 and urinary protein was increased in males at week 26 and in females at week 52; high levels of GOT and ALP for males and females were evident at weeks 26 and 52. Increased thyroid weight in both sexes at 2000 ppm was recorded at weeks 26 and 52, and in males at 200 ppm at 52 weeks only. At 52 weeks, males and females at 2000 ppm showed splenic congestion and dilatation of sinuses and increased brown pigment deposition in the renal tubular cells at 52 weeks.

Mouse

In the carcinogenicity study (Harada, 1992), groups of ICR (Crj:CD1) mice were fed diets containing MCPA- thioethyl at 0, 30, 300 or 1500 ppm in the diet, equivalent to 0, 2.8, 29.3 or 151 mg/kg bw/day. An interim kill of 20 mice/sex/group was conducted at 52 weeks. At 1500 ppm there was decreased body weight throughout the 52 weeks; at 300 ppm, there was a slight but consistent decrease in body weight and food efficiency. There was no significant treatment related histopathology and the NOAEL was 30 ppm (2.8 mg/kg bw/day).

There were two non-GLP 90 day dietary toxicity studies with MCPA-thioethyl in mice (Morrow *et al.*, 1974; Shirakawa, 1973). These studies examined doses of 0, 1.4, 7, 35 and 150 mg/kg bw/day (Morrow *et al*., 1974) and 0, 3.9, 13.1, 39 and 141 mg/kg bw/day (Shirakawa, 1973). In agreement

with Harada (1992) there was no evidence of specific target organ toxicity. Mice fed at 150 mg/kg bw/day did not gain weight as much as control during most of the study (Morrow *et al.*' 1974). Additional reported findings were: discoloration of the liver at 150 mg/kg bw/day (Morrow *et al*., 1974); a marked increase in GOT in the 30 mg/kg bw/day group and changes in cranial nerves in female mice in the 141 mg/kg bw/day group. (Shirakawa, 1973). These findings, which were not seen in the subsequent 1 year study at similar doses are considered to be unrelated to treatment with MCPA-thioethyl.

Dog

A 13-week feeding study was carried out to examine the subchronic toxicity of MCPA in beagle dogs. No specific internationally recognised protocol was followed and it was not GLP compliant. Four dogs per sex per group received 0, 3, 12 or 48 mg MCPA (94.6% pure)/kg bw/day in the diet and an additional study four animals per sex per group received 0, 0.3, 1.0 or 12 mg technical grade MCPA (99.25%)/kg bw/day and 12 mg of purified MCPA/kg bw/day (MCPA.P). Ophthalmoscopy, haematological, clinical chemistry and urinalysis were carried out before the beginning, in the mid and at the end of the study. Health condition and behaviour of all dogs were checked daily. Additionally, faecal blood content was examined. A liver function test (bromosulphophthalein (BSP) method) and a kidney function test (phenolsulphophthalein (PSP) method) were conducted at week 13. All animals were assessed by gross pathology, organs were weighed and histopathology was performed. At 48 mg/kg bw/day there were severe clinical symptoms and one dog died and the remainder were killed in a moribund state. Food consumption was markedly reduced and weight loss occurred at this dose level. Clinical changes consisted of pustules, papules, necrotic skin lesions, focal stomatitis, conjunctivitis, diarrhoea, anorexia, dehydration, lethargy and signs of icterus. Muco purulent conjunctivitis was also found in a few dogs fed 12 mg/kg bw/day MCPA or MCPA.P. Weight gain of the dogs fed 12 mg/kg bw/day was decreased. A variety of changes in haematology, clinical chemistry and urinalysis were noted. Blood urea values were slightly increased in males and females fed 3 mg MCPA/kg/day or more and in dogs fed 12 mg/kg bw/day MCPA.P. High creatinine and GPT values were found in the blood of dogs at 3, 12, 48 mg/kg bw MCPA/day and 12 mg/kg bw MCPA.P/day. Glucose values were decreased in dogs fed 48 mg/kg bw/day. Elevated bilirubin and OCT values and low albumin and protein values occurred in some dogs fed 48 mg/kg bw MCPA/day prior to death. The Na+ and K+ contents in the urine of dogs at 48 mg/kg bw MCPA/day were generally lower than in controls. Bilirubin was detected in urine of some dogs fed 48 mg/kg bw MCPA/day. Kidney function was adversely affected in dogs fed 3, 12, 48 mg/kg bw MCPA/day and in dogs fed 12 mg/kg bw MCPA.P/day. Liver function was affected in the surviving dog of the high-dose group. Faecal blood was recorded in 48 mg/kg bw MCPA/day group and in two of the dogs fed MCPA.P. The relative kidney weights were increased (high dose) and the prostate weights reduced in dogs fed 12 mg/kg bw MCPA/day. Gross pathological examination revealed jaundice, enlarged gall bladder, haemorrhages in the intestine, stomach, and lungs, pale livers, a tan-coloured liver and a swollen, yellow liver in the high-dose group. Enlarged gall bladders were found in 2 dogs fed 12 mg/kg bw MCPA/day. Degenerative and/or regenerative changes were found in the liver, kidneys and gastro-intestinal tract of dogs fed 48 mg/kg bw MCPA/day. Dogs fed 12 mg/kg bw MCPA/day showed a slight increase in incidence and degree of infiltrates of mononuclear cells in the liver. Slight to moderate bile duct proliferation was noted by histopathology in some dogs fed 12 mg/kg bw MCPA/day or MCPA.P. Increased creatinine values, alanine aminotransferase activity and blood urea values were found in the dogs of the 3 and 12 mg/kg bw/days groups. Kidney function was impaired in the animals of these groups. No difference in toxicity could be established between MCPA technical product and purified MCPA. All further examinations as well as gross pathology and

histopathology revealed no treatment-related changes of any toxicological relevance. It was concluded the NOEL was 1 mg/kg bw/day for both sexes. (Reuzel, 1980).

In a non-GLP 2 year dog study, groups of 4 male and 4 female beagle dogs received 20, 100 or 500 ppm MCPA-thioethyl in the diet for 24 months. Body weights in males at 500 ppm were reduced from 4th week throughout the study with a maximum reduction during weeks 13-16. No unusual behavioural reactions were seen at any dose throughout the study. After 14 weeks of treatment, one animal at 500 ppm had a depressed erythrocyte count, haemoglobin, haematocrit as well as an elevated serum GPT value. This animal was terminated and at autopsy, gross pathological examination revealed pale intestines and pale and oedematous lungs. Female dogs at 500 ppm showed a slight depression of erythrocyte count, haemoglobin, haematocrit between 3 and 12 months of treatment. Males at this dose showed a reduced haemoglobin concentration between 3 and 12 months. Histopathological evaluation of tissues indicated the presence of treatment-related morphological changes in the liver and kidneys at 100 and 500 ppm. The primary lesion in the liver was extramedullary hematopoiesis. This lesion was multifocal in distribution among animals at 500 ppm and was graded minimal to moderate in severity. In the kidneys the pigments were present at the level of the convoluted tubules. The NOEL was tentatively set at 20 ppm, equivalent to approximately 1.0 mg/kg bw/day, based on the presence of pigments in liver and kidneys. (Mastalski, 1976.)

4.7.1.2 Repeated dose toxicity: inhalation

No inhalation repeated dose toxicity study has been conducted, nor is considered warranted, since MCPA-thioethyl has low vapour pressure and it is anticipated that there will be very low exposure during normal agricultural use.

4.7.1.3 Repeated dose toxicity: dermal

A repeated dermal toxicity study with MCPA was performed in male and female New Zealand White rabbits to assess the cutaneous and systemic toxicity. MCPA was moistened with distilled water and dermally applied once a day over a period of approximately six hours to groups of five males per dose group for 21 consecutive days or to five females per dose group for 22 consecutive days. After 6 hours the dressings were removed and the treated skin washed with warm water and gently blow-dried. The dose levels were 10, 100 and 1,000 mg/kg bw/day. A group of five male and five female rabbits served as control and received distilled water. The treatment area for all animals was a shaved region of the back that represented approximately 10% of the total body surface. Dermal responses were recorded before the first application and subsequently on a daily basis. Dermal reactions were scored according to the Draize method. Blood samples for haematological examinations and clinical chemistry were taken from fasted animals and urine samples were collected overnight prior to termination. Necropsy was performed on all sacrificed animals, gross observations were recorded, organs were weighed and tissues were examined histopathologically. No mortalities or treatment-related clinical signs were seen. Body weight and food consumption, haematology, biochemistry, urinalysis, organ weight, and macroscopic pathology were not affected in any group. The repeated application of MCPA caused cumulative irritation in a dose-dependent severity in male and female rabbits at the application sites. At 1000 mg/kg bw/day erythema and oedema progressing from slight to well-defined was recorded in 5/10 animals by day 10. Additionally, discoloration, dryness and desquamation occurred in a varying incidence. Histopathologically minimal diffuse acanthosis with or without hyperkeratosis of the treated skin was recorded in all animals at this dose group. At 100 mg/kg bw/day slight erythema and oedema in a varying degree and intensity were noted and minimal diffuse acanthosis occurred also in some animals. At 10 mg/kg bw/day no skin reactions were noted. All other examinations revealed no further substance-related findings. It was concluded that the

NOEL for systemic toxicity was 1000 mg/kg bw/day, while the NOEL for dermal irritation was 10 mg/kg bw/day. (Baldrick et al, 1992)

4.7.1.4 Repeated dose toxicity: other routes

No further information available

4.7.1.5 Human information

No information

4.7.1.6 Other relevant information

No further relevant information.

4.7.1.7 Summary and discussion of repeated dose toxicity

The sub-chronic toxicity profile of MCPA-thioethyl and MCPA has been investigated in the rat, mouse and dog (oral route) and rabbit (dermal route).

In the rat, oral toxicity has been evaluated in 90-day studies and at 12 months in combined chronic toxicity/carcinogenic studies. In the 90 day studies with MCPA (Kirsch, 1985; Mellert et al 1994b), effects at doses of 177 mg/kg bw/day include: reduced body weight and food consumption, decreases in some behavioural measures (fore and hind-limb grip strength, landing foot splay, motor activity); haematological changes consistent with macrocytic anaemia and in female only, reduced leucocyte count and prolonged prothrombin time; reductions in triglycerides; differences in absolute or relative organ weights (liver increased in females, kidney increased in males; lower relative adrenal weights (females), lower testes weights); marked hepatocellular cytoplasmic eosinophilia and granular cytoplasm; minimal to moderate foam cells in the lung of males and females; hypercellularity of the bone marrow, consistent with impaired red cell production; increased lipid in adrenals; diffuse atrophy of the testes (severe to extreme) in all males with oligozoospermia and aspermia in 3 and 7 rats, respectively; thymic atrophy in 3 females (Mellert et al, 1994b). At a dose of 34/37 mg/kg bw/day effects reported were: lower body weight gain (Mellert et al, 1994b), reduced serum triglycerides (Mellert et al, 1994b); increased creatinine and reduced cholesterol and calcium levels (Kirsch, 1985); increases in kidney weights (Mellert et al, 1994b, Kirsch, 1985); lower relative adrenal weights (females) and testes weights and increased lipid in adrenals (Mellert et al, 1994b). At 12 mg/kg bw/day the only effect reported was increases in kidney weights (Kirsch, 1985). No effects were seen at doses of 4.1 (Kirsch, 1985) or 3 mg/kg bw/day (Mellert et al, 1994b). Lower body weight gain and haemolytic anaemia was also seen at a dose of 78.7 mg/kg bw/day after 13, 26 and 52 weeks in the chronic toxicity phase of the 2-year study with MCPA (Maita, 1988). In addition, reduced thyroid weight, splenic congestion, dilatation of sinuses and increased brown pigment deposition in the renal tubular cells were seen at 52 weeks at this dose. At 7.7 mg/kg bw/day males showed slightly lower body weight and increased thyroid weight at 52 weeks (Maita, 1988).

In 90-day studies with MCPA-thioethyl (Morrow, 1974; Shirakawa, 1973) similar dose levels have been examined. At 150 mg/kg bw/day the effects included: reduced body weight gain and reduced food consumption; evidence of anaemia; clinical chemistry effects, possibly related to the weight loss; haemosiderin deposits in the spleen; pigments in the kidney cortex tubules (Morrow, 1974). In this study there were no effects at 35 mg/kg bw/day. In contrast, Shirakawa (1973) reported atrophy of splenic lymphatic follicles, decreased spermatogenesis and atrophy of nerve cells in the spine and brain stem at both 57 and 19 mg/kg bw/day and decreased spermiogenesis and atrophy of spinal cells

and neurocytes in the brain stem at 8.2 mg/kg bw/day. No effects were seen at doses of 1, 4 or 7 mg/kg bw/day in the Morrow (1974) study and Shirakawa (1973) had a no effect level of 1.4 mg/kg bw/day.

In mice, toxicity of MCPA-thioethyl has been assessed after 90 days (Morrow, 1974; Shirakawa, 1973) and 52 weeks (Harada, 1992). The high dose level of ~150 mg/kg bw/day induced a decrease in body weight gain (Morrow, 1974; Harada, 1992). There was no significant treatment related histopathology seen in the Harada, 1992 study at 52 weeks, whilst an increase in splenic haemosiderin deposits and discoloured livers were seen in one of the 90 day studies (Morrow, 1974) and changes in the cranial nerve system of female mice were seen in the other (Shirakawa, 1973).

In the Harada, 1992 carcinogenicity study in ICR (Crj:CD1) mice, at 1500 ppm there was decreased body weight throughout the 52 weeks; at 300 ppm, there was a slight but consistent decrease in body weight and food efficiency.

Data from a 90-day dog study with MCPA and a 2-year study with MCPA-thioethyl (both dietary administration) are available. In the 90-day study (Reuzel, 1980), the top dose of 48 mg/kg bw/day was clearly in excess of the MTD with one dog being found dead and 6/7 remaining dogs being killed in a moribund state. These dogs showed severely reduced body weight gain and reduced food consumption and exhibited a range of adverse clinical signs. In the 2-year study (Mastalski, 1976) the top dose of approximately 25 mg/kg bw/day elicited reduced body weight, anaemia and histopathologically there was extra-medullary haemopoiesis in the liver and pigmentation in kidney tubules. One dog was killed at week 14 due to the severity of the effects. At 12 mg/kg bw/day in the 90 day study (Reuzel, 1980), dogs showed reduced body weight gain and adverse changes in haematology and clinical chemistry parameters; there were effects on kidney function and an increase in incidence and degree of infiltrates of mononuclear hepatocytes. At 3/5 mg/kg bw/day there was evidence of liver and kidney toxicity at both 90 days and 52 weeks (Reuzel, 1980; Mastalski, 1976).

In a dermal study, with MCPA; there were dose related topical changes at 100 and 1000 mg/kg bw/day but no evidence of systemic toxicity at any treatment level.

These studies demonstrate that MCPA/ MCPA-thioethyl induced toxicity by the oral route to rats, mice and dogs. MCPA induced some local effects in the rabbit via the dermal route but there was no evidence of systemic toxicity.

4.8 Specific target organ toxicity – repeated exposure (STOT RE)

STOT-RE relates to specific target organ toxicity following repeated exposures to a substance (or mixtures). Specific toxic effects covered by other hazard classes are not included in STOT-RE. Specific toxic effects include consistent and identifiable effects in humans or experimental animals and toxicological significant changes which affect the function or morphology of an organ or tissue and which has relevance for human health.

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

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

In the rat, the principle 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 and above although this was not allied to histopathological changes. In the Morrow 1974 study with MCPA-

thioethyl, splenic haemosiderin pigments were evident at 150 mg/kg bw/day 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/day) and above. The subacute neurotoxicity study (Mellert et al, 1994b) reported reduced grip strength in rats at 2500 ppm (177 mg/kg bw/day). The main change in this study was evidence of haemolytic anaemia at 2500 ppm (177 mg/kg bw/day). Kidney weights were significantly increased at 500 ppm (34 mg/kg bw/day) and above, but there was no histopathology. There was increased lipid in adrenals at 177 and 34 mg/kg bw/day. Data from the interim kills from the carcinogenicity studies confirmed a haemolytic anaemia and splenic congestion at high doses (approximately 78 mg/kg bw/day).

In the mouse studies (both conducted with MCPA-thioethyl) Morrow, 1974 reported increased splenic haemosiderin deposits at 150 mg/kg bw/day, whilst Shirakawa reported changes in the cranial nerve system of female mice (only) at 1000 ppm (equivalent to 150.3 mg/kg bw/day). 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, decrease liver and kidney function with degenerative/ regenerative changes in the liver, kidneys and gastro-intestinal tract were seen at 48 mg/kg bw/day (Reuzel, 1980). At 12 mg/kg bw/day, 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/day. In the 2-year study, the principle 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/day.

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

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

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 (Guidance Value Ranges: $10 < C \leq 100$ mg/kg bw/day in 90 day oral rat studies; $30 < C \leq 300$ mg/kg bw/d for 28 day data; $2.5 < C \leq 25$ mg/kg bw/day for 1 year data) or Category 1 (Guidance Value Ranges: $C \leq 10$ mg/kg bw/day in 90 day oral rat studies; $C \leq 30$ mg/kg bw/day for 28 day data; $C \leq 2.5$ mg/kg bw/day for 1 year data).

Treatment–related effects were seen in a variety of tissues (spleen, haematological system, kidney, nervous system, testes, liver and gastrointestinal tract) in rats and dogs. The following summary focusses on effects that are relevant for consideration for classification.

Spleen

Haemosiderin deposits were seen in the 90-day rat studies (Morrow, 1974 and Shirakwa, 1973) at 57 mg/kg bw/day and above and in the 90 day mouse study at 150 mg/kg bw/day (Morrow, 1974). In these 90 day studies, haemosiderin deposits in the spleen were observed where there was treatment-induced haemolytic anaemia (as was observed in the Morrow, 1974 study). All these studies were 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 treated 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/day; similarly

there was no evidence of spleen effects in the sub-chronic neurotoxicity study (Mellert et al, 1994b) at the top dose equivalent to 177 mg/kg bw/day. At the 52 week kill in the rat carcinogenicity study (Maita, 1988) the top dose of 2000 ppm (equivalent to 78 mg/kg bw/day) 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 mixed. There was no evidence of spleen effects in the two 90-day studies, but there was evidence of an effect at the interim kill in the carcinogenicity study at 78.7 mg/kg bw/day. This is above the Guidance Value for Category 2 classification for 1 year data ($2.5 < C \leq 25$ mg/kg bw/day for 1 year data) and therefore no classification is required.

Haematological Parameters

A number of studies in the rat and dog showed changes in haematological parameters indicative of anaemia. In the rat, there was evidence of a haemolytic anaemia at 78.7 mg/kg bw/day 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/day. There was no consistent evidence for anaemia in the mouse, dog or rabbit.

The haemolytic anaemia at week 13 in the carcinogenicity study at 78.7 mg/kg bw/day, 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.

Kidney

Kidney weights were increased at 12 mg/kg bw/day and above in the Kirsch et al, 1985 90 day rat study, and for males in the sub-acute neurotoxicity study (Mellert et al, 1994b) at 34 mg/kg bw/day. In the 90 day dog study (Reuzel et al, 1980) kidney function was reported to be affected at 3 and 12 mg/kg bw/day. None of these changes were accompanied by pathological damage and are therefore, considered not to indicate significant target organ damage. At 48 mg/kg bw/day in the dog study there were reported degenerative changes in the kidney. However, this dose level was systemically toxic with 7/8 dog dying or killed due to the severity of clinical findings. There were no changes in the mice or rabbit studies.

As the only evidence of degenerative kidney changes in the dog were seen at a dose level associated with significant general toxicity and morbidity and are not relevant for classification as STOT RE. No classification is required.

Nervous System

The primary study for consideration of effects on the nervous system is the sub-acute study in rats (Mellert et al, 1994b); apart from decreased grip strength at the top dose of 177 mg/kg bw/day (which may have been a consequence of the significant decreased bodyweight effect), there was no evidence of neurological changes. 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/day; the corresponding mouse study (Shirakawa, 1973) reported changes (unspecified) in the cranial nerve system in female mice at 150 mg/kg bw/day. In the light of the age of these studies (pre-GLP and the adoption of accepted regulatory protocols) these results must be treated with caution and priority 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 required.

Testes

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.

No effects were reported in mice, dogs or rabbits.

As reported above, the effects reported in the rat by Shirakawa should be treated with caution owing to the age of the study. However, the potential for MCPA-thioethyl and MCPA is supported by the effects seen in the regulatory 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/day 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. In addition, effects on the testes should be considered for classification as a reproductive toxicant. However, in three studies (including one, two and three generation reproduction studies) neither MCPA-thioethyl nor MCPA was found to induce any effects on fertility, reproduction, pregnancy outcome or littering in the rat (see 4.11). Consequently MCPA-thioethyl does not meet the criteria for classification as STOT-RE or as a reproductive toxicant.

Liver

In the sub-acute neurotoxicity study (Mellert, 1994b) at 177 mg/kg bw/day there was a liver weight increase and pathology showed marker hepatocellular cytoplasmic eosinophilia and granular cytoplasm. In the 90 day dog study (Reuzel et al, 1980), at 12 mg/kg bw/day there was a slight increase in the incidence and degree of infiltrates of mononuclear cells in the liver and at 48 mg/kg bw/day there were degenerative/ regenerative changes.

No liver effects were reported for mice or rabbits. Effects seen at doses associated with severe systemic toxicity are not relevant for classification for STOT-RE. The minor effects at 12 mg/kg bw/day in the dog study (slight increase in the incidence and degree of infiltrates of mononuclear cells) are considered not to represent significant target organ toxicity. The effects in the rat study were outside the Guidance Value Ranges: $10 < C \leq 100$ mg/kg bw/day and consequently no classification is required.

Gastro-Intestinal Tract

In the 90-day dog study (Reuzel et al , 1980) at 48 mg/kg bw/day there were haemorrhages in the intestine and stomach; pathology revealed degenerative/ regenerative changes in the gastro-intestinal tract. This dose level was very toxic to the dog; one dog died and six others, were killed in a moribund state. The dogs showed a myriad of effects and it is considered likely that these gastro-intestinal effects were secondary to the primary toxic response.

There were no effects reported in the rat, mouse or rabbit.

No classification for STOT RE effects on the gastro-intestinal tract is required.

Other effects were either at a dose above the Guidance Value for classification, or of an unreliable nature (e.g. weight changes without histopathological correlates).

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

CLP: STOT RE: No classification

4.9 Germ cell mutagenicity (Mutagenicity)

Table 16: Summary table of relevant in vitro and in vivo mutagenicity 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. (Purity: IUCLID technical dossier)	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 andwas 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. 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.	Shirasu, no date
In vitro bacterial reverse mutation assay	Negative, with and without metabolic activation. This report is confidential proprietary information.	Thompson, 2014*
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/kgbw MCPA-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*

* Key studies for consideration of MCPA-thioethyl classification

4.9.1 Non-human information

4.9.1.1 In vitro data

Bacterial Assays for gene mutation: Shirasu (no date) reported the conduct and results of a rec-assay, reverse mutation assay and a host-mediated assay. In the 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.

In the 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.

In the 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.

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.

This conclusion was supported by a recent study: Thompson, 2014 which is summarised in full and referenced as 'Confidential' in the accompanying IUCLID file.

Chromosome test in mammalian cells: In a Chinese hamster V79 test, there was no inhibition of cell growth up to the highest concentration tested, which was a limit dose of 10mM (2.4mg/ml). 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 incubation. Cells were arrested in metaphase by the addition of colchicine two hours before harvest, and 100 metaphases were scored blind. MCPA-thioethyl, with or without metabolic activation, did not significantly induce chromosomal aberrations at any of the concentrations tested. (Shibuya, 1984). However, the positive controls induced clear increases in chromosomal aberrations.

Mammalian cell gene mutation: The effects of MCPA-thioethyl on the induction of forward mutations at the thymidine-kinase locus (TK-locus) in L5178Y mouse lymphoma cells in the presence and absence of S9-mix were investigated, examining for both large and small colonies. The test was performed in two independent experiments in the presence and absence of S9-mix (Aroclor-1254 induced rat liver S9-mix). MCPA-thioethyl precipitated at the dose level of 17 µg/mL and upwards in the exposure medium.

In the first experiment, 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 times were 24 hours and 3 hours for incubation in the absence and presence of S9 metabolic activation system respectively. Toxicity was observed at this dose level only in the presence of S9-mix.

The positive control substance in the absence of S9 mix was ethyl methanesulphonate (EMS), and in the presence of S9 was dimethylnitrosamine (DMN).

MCPA-thioethyl did not induce a significant increase in the mutant frequency in the absence or presence of S9 metabolic activation in the first experiment. This result was confirmed in a second, repeat experiment with modifications in the duration of treatment in the absence of S9 (exposure 3 hours in the first experiment and 24 hours in the second experiment), and in the S9 concentration for metabolic activation (8% in the first experiment, 12% in the second experiment).

Mutant frequencies in cultures treated with positive control chemicals were increased significantly in both experiments. It was therefore concluded that the test conditions, both in the absence and presence of S9-mix, were appropriate and that the metabolic activation system (S9-mix) functioned properly. (Verspeek-Rip, 2002).

It is concluded that MCPA-thioethyl is not mutagenic in the mouse lymphoma L5178Y test system under the experimental conditions described in this report.

4.9.1.2 In vivo data

Micronucleus test in bone marrow cells: Six groups each comprising 5 male and 5 female NMR1: BR mice, received a single oral intubation of 500 mg/kg bw (2 groups), 250 mg/kg bw and 125 mg/kg bw MCPA-thioethyl. The top dose was a maximum tolerated dose based on toxicity seen in a dose ranging study. A vehicle treated group served as negative control and a group treated with a single oral intubation of 50 mg/kg bw cyclophosphamide served as positive control. Bone marrow of the groups treated with MCPA-thioethyl was sampled 24 (all dose groups) or 48 hours (top dose group only) after dosing. Bone marrow from the negative control group was harvested at 24 hours after dosing only and bone marrow from the positive control group was harvested at 48 hours after dosing only.

Animals dosed with 500 mg/kg bw MCPA-thioethyl showed clinical signs of lethargy and ataxia and 3 male animals also had a rough coat. There were no clinical abnormalities in animals dosed with 250 or 125 mg/kg body weight.

Cyclophosphamide induced a statistically significant increase in the number of micronucleated polychromatic erythrocytes in both sexes. No increase in the frequency of micronucleated polychromatic erythrocytes was observed in the polychromatic erythrocytes of the bone marrow of MCPA-thioethyl treated animals compared to the vehicle treated animals.

A significant decrease in the ratio of polychromatic to normochromatic erythrocytes, indicating a toxic effect of MCPA-thioethyl on erythropoiesis, was seen in animals treated with 500 mg MCPA-thioethyl/kg body weight for 48 hours and in animals in the positive control group. There was no decrease in the ratio of polychromatic to normochromatic erythrocytes in animals treated with 500 mg MCPA-thioethyl/kg body weight for 24 hours, those treated with 250 or 125 mg/kg bodyweight, or in the negative control animals (Meerts, 2002).

It is concluded that MCPA-thioethyl is not mutagenic in the micronucleus test under the experimental conditions described in this report.

4.9.2 Human information

No information

4.9.3 Other relevant information

No information.

4.9.4 Summary and discussion of mutagenicity

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.

4.9.5 Conclusions on classification and labelling

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.

CLP: No Classification

4.10 Carcinogenicity

Table 17: Summary table of relevant carcinogenicity 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 leukaemia 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 toxicological NOEL was 0.95 mg/kg bw/day.**	Maita, 1988*
Rat: Wistar Carcinogenicity- chronic toxicity (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	No compound-induced benign or malignant tumour incidence was noted at any dose level. **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).**	Kirsch et al. 1988

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. **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**	Kűhborth et al, 1988

* Key studies for consideration of MCPA-thioethyl classification

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

Rat

Groups of 80 Fisher Rats (F344/DuCrj) received 0, 20, 200 or 2000 ppm (corresponding to 0.95, 9.3 and 98.5 mg/kg bw/day) MCPA-thioethyl in the diet for 24 months. Ten animals/sex/group were subjected to haematology after 13 weeks of treatment and to urinalysis, haematology, blood biochemistry, and pathology after 26, 52 and 78 weeks of treatment. After 104 weeks of treatment, clinical pathological examinations were performed on 10 animals/sex/group, and all surviving animals were examined pathologically. The mortality rate did not increase in the animals treated with MCPA-thioethyl. There was no increased incidence in tumours in treated groups compared to controls. At 2000 ppm males and females showed a decreased incidence of mononuclear cell leukaemia, which resulted in a decreased mortality in males. Both sexes exhibited a decreased body weight gain throughout the study (3-6% for males, 3-12% for females). Urinalysis showed decreased urine protein in both sexes and increased urine volume in females. Anaemic changes in both sexes were observed. High levels of GOT, GPT, ALP and BUN and a low level of glucose were found in both sexes. At autopsy, increased thyroid weight in both sexes, an increasing trend of kidney weights in males, and increased spleen weights in females were observed. Dark coloured kidneys and spleen (both sexes) as well as hair loss in the skin and around the eyelid of females were seen. Histopatologically, 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. At 200 ppm, males showed slightly lower body weights during the first half of the treatment period compared to the control. Increased thyroid weights were seen in both sexes. Females showed increases in urine volume and serum creatinine. A higher incidence of microscopical lesions, increased brown pigment deposition in the renal tubular cells, was seen in males. It was concluded that MCPA-thioethyl is not carcinogenic to the rat under the conditions of this study: the toxicological NOAEL was 20 ppm (equivalent to 0.95 mg/kg bw/day). (Maita, 1988)

The chronic toxicity and the potential carcinogenicity of MCPA (94.8%) was investigated in Wistar rats. MCPA was administered in the diet at concentrations of 0, 20, 80 and 320 ppm for a period of 24 months (corresponding, approx. to 1.25, 5 and 20 mg/kg bw/day). Dose and control groups were separated into a main group and satellite groups I and II; haematology and clinical chemistry was performed five times in satellite group II, while urinalysis was carried out twice in satellite group I animals after approximately half a year and a year, and in ten rats of each main group after approximately 24 months. The feed consumption and body weight of the animals in the main groups and of satellite groups I was determined once a week up to 14 weeks and thereafter once a month until the end of the study. The state of health of all animals was checked daily; furthermore, the animals were subjected to additional inspection and palpation once a week. Ophthalmology was conducted at the beginning and subsequently every six months in the control and top dosed rats of the main group. Survivors in satellite group I, in satellite group II and in the main group were killed after 12 and 24 months respectively. Gross pathology and histopathological examinations were performed on all animals. MCPA did not elicit any adverse clinical signs attributable to the substance. At 320 ppm there was reduced body weight gain of up to 9% in males, increased ALT activity in females and decreased triglyceride values in both sexes. Plasma ALT activities were significantly increased in female animals at 320 ppm after 12-, 18-and 24-month administration. ALT activity was also increased at 12 months for 80 ppm female animals but not at 18 and 24 months. Other examinations regarding substrates, enzymes, blood clotting parameters and urine parameters as well as hormones revealed no changes attributable to the test substance administered. Histopathological

(non-neoplastic) changes were noted in the kidneys and spleen of the males at 320 ppm. These findings consisted of a progressive nephropathy associated with increased kidney weights and increased haemosiderosis in the spleen. The relative liver weight of the females showed a significant (20 ppm) or highly significant (320 ppm) decrease. Group 2 (80 ppm) showed no statistical deviation. Since there were no histological findings in the liver related to the application of the test substance, the change in liver weight is regarded as being of no toxicological significance. At 80 ppm, sporadically increased values for triglyceride in both sexes and ALT activity in females were noted, while no substance-related findings were found at 20 ppm. No compound-induced benign or malignant tumour incidence was noted at any dose level. It was concluded that no carcinogenic effect was observed in this study and the NOEL for chronic toxicity in male and female Wistar rats was 20 ppm (approx. 1.3 mg/kg bw/day). (Kirsch, 1988).

Mice

Groups of 50 males and 50 females SPF ICR (Crj:CD-1) mice received 30, 300 or 1500 ppm of MCPA-thioethyl in the diet (corresponding to 2.8, 29.3 and 151 mg/kg bw/ day) for 18 months. A satellite study, using 20 males and 20 females for each group was terminated after 52 weeks. The animals of both sexes receiving 1500 ppm showed slightly (within 10 %) but consistently lower mean body weight than controls throughout the treatment period; a statistically significant decrease was observed in males from week 1 to week 16 and in females from week 3 to week 52. The average food efficiency, evaluated during the first 13 weeks, for males and females was respectively 10% and 19 % lower compared to the controls. The animals treated with MCPA-thioethyl did not exhibit any differences from the controls in terms of mortality. Clinical signs observed were considered incidental and not related to treatment. At 300 ppm and above, there was a slight but consistent decrease in growth and food efficiency which may have been due to MCPA-thioethyl treatment. Haematological examinations revealed no treatment-related changes in both sexes. At 1500 ppm there were signs of hepatotoxicity (dark coloured livers and increased brown pigment deposition in Kupfer cells). There was no evidence of carcinogenic activity of MCPA-thioethyl at any dose for 78 weeks. MCPA-thioethyl was not carcinogenic to mice under the conditions of this study. The NOEL for toxicity was 30 ppm, corresponding to 2.8 mg/kg/day. (Harada, 1992).

The chronic toxicity and carcinogenicity of MCPA (94.8%) was investigated in male and female B6C3F1 mice (Kűbborth, 1988). Mice were exposed to MCPA in the diet for 104 weeks at dose levels of 0, 20, 100 and 500 ppm. Each group was divided into one main group (50 animals per sex) and one satellite group (ten animals per sex). Sixty animals of each sex were used as controls, divided between the main and satellite group. Blood for haematology was obtained from the satellite group after about 52 weeks and thereafter the animals were sacrificed. At termination blood samples were taken from each ten animals of the main group, all animals were assessed by gross pathology, organs were weighed and subsequently a histopathological examination was performed. There were no treatment-related effects in mortality, state of health, bodyweight and food consumption in any group.

The DAR reports that MCPA induced signs of nephropathy at the top dose of 500 ppm; as this applicant has not been given access to the report or data for this study, no further comment on this reported effect can be made. The absolute and relative kidney weights were increased in female rats and histopathology revealed an increased incidence of intratubular calcification and hyaline casts in both sexes. A tubular epithelial hyperplasia was observed in the males.

In the males of the 100 and 500 ppm groups there was only an intermittent trend of a reduction of the body weight gain from the 3rd week up to 1 year of treatment. This effect was not observed in the corresponding satellite groups. An increased number of lymphocytes with changes to the nuclear structure after 104 weeks of test substance administration was only seen in the differential blood count of the males of 100 ppm group and the females of 500 ppm group. The finding in males was not dose-dependent and considered unrelated to treatment; the increase in the number of atypical lymphocytes was observed in 7/ 10 females of the 500 ppm group (v 2/9 for control animals, 3/10 and 0/10 for 20 ppm and 100 ppm groups respectively). No remarkable variations of the red blood count were seen in the treated main group animals. An increase in the Howell-Jolly bodies in the females dosed 500 ppm (5/10 animals) could be indicative of a marginal adverse effect of the test substance on the red blood cells, especially since some animals of this test group showed other morphological changes of the erythrocytes. In females dosed 100 and 500 ppm there was a significant decrease in the absolute and relative heart weights. Further in male group 500 ppm a decrease in relative testes weight was found. Since there are neither histological findings in the heart and testes related to the administration of the test substance, nor a dose-dependency for the heart, the changes in organ weights are not considered to be of biological relevance. No further substance-related effect in any dose group and no compound-induced increase in benign or malignant tumour incidence was noted. It was concluded that MCPA has no carcinogenic potential in B6C3F1 mice and 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).

4.10.1.2 Carcinogenicity: inhalation

Not relevant as MCPA-thioethyl is not volatile.

4.10.1.3 Carcinogenicity: dermal

No information.

4.10.2 Human information

Although a limited number of epidemiological studies have been conducted on the effects of MCPA and related chlorophenoxy compounds, 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. The outcome of a few of these studies is given below.

Coggon et al. (1986) examined the mortality of 5754 workers involved in manufacturing and spraying of MCPA and other phenoxyacetic acid herbicides from 1947 to 1975 in England. Overall mortality (including that from cancer, heart disease and respiratory disease) was less than that of the national population. One soft tissue sarcoma was detected against the expected 0.6. The authors concluded that any risk of soft tissue sarcoma due to MCPA is less than suggested by earlier studies of 2,4,5-T and 2,4,5-trichlorophenol production and must be small in absolute terms.

A study of cancer incidences among 4459 Danish workers involved in the production of MCPA and other phenoxyacetic acid herbicides was undertaken by Lynge et al. (1985). The overall cancer incidence among workers was unremarkable, with the exception that 5 soft tissue sarcomas were detected in males versus an expected 1.84 for the Danish population. The 5 soft tissue sarcomas were all different tumour types, and only one case was linked directly to manufacturing. The study did not differentiate between exposure to different pesticides and exposure to precursor chemicals involved in their production.

Wiklund & Holm (1986) investigated the risk of soft tissue sarcoma in 354 620 Swedish male agricultural or forestry workers (identified in the 1960 census) due to exposure to phenoxyacetic acid herbicides. A reference cohort of 1 725 845 Swedish men involved in other industries was used as the comparator. In total, 331 cases of soft tissue sarcoma were detected versus 1508 in the reference cohort (relative risk = 0.9; 95% confidence interval [CI] = 0.8–1.0), which indicated that there was no increase in cancer risk. In a follow-up study by Wiklund et al. (1987), the risk of Hodgkin disease and non-Hodgkin lymphoma in a cohort of 20 245 Swedish pesticide applicators was studied. Seventy-two per cent were estimated to have used phenoxyacetic acid herbicides. Eleven cases of Hodgkin disease (versus an expected 9.1 in the general population; rate ratio = 1.20, 95% CI = 0.6–2.16) and 21 cases of non-Hodgkin lymphoma (versus an expected 20.8 in the general population; rate ratio = 1.01, 95% CI = 0.63–1.54) were detected, with no significant increase in the risk of either malignant lymphoma.

4.10.3 Other relevant information

No further relevant data.

4.10.4 Summary and discussion of carcinogenicity

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. Although a limited number of epidemiological studies have been conducted on the effects of MCPA and related chlorophenoxy compounds, 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.

4.10.5 Comparison with criteria

The criteria for Category 1 (Known or Presumed Human Carcinogen) is based on human evidence or on animal data where there is sufficient evidence to demonstrate animal carcinogenicity.

Category 2 (Suspected Human Carcinogen) is based on human evidence and/or animal data where there is insufficient data to place the compound into Category 1, but there may be limited data from human or animal studies of an effect.

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.

4.10.6 Conclusions on classification and labelling

CLP: No classification

4.11 Toxicity for reproduction

Table 18: Summary table of relevant reproductive toxicity studies

Method	Results and Remarks	Reference
3-generation reproduction (2 litters per generation) Rat: Charles River, albino Guideline: not stated but does not meet current requirements GLP: No Test Material: MCPA-thioethyl (phenothiol) (purity not stated) Treatment: continuous in the diet at 0, 20, 100 or 500 ppm F0 – 10 males and 20 females per group, allowed to reach maturity and then mated to produce 2 litters. 10 males and 20 females / group selected from the second litter to produce the next generation. Study terminated following weaning of F3b. Parental growth and condition recorded. Reproductive performance and litter parameters monitored. Organ weights collected. Gross autopsy of parents (8/sex/group) after weaning of second litter; microscopic examination of tissues from 5/sex control and high dose parents.	**500 ppm, 100 ppm and 20 ppm (approximately 25, 5 and 1 mg/kg bw/day):** no effect on growth, food consumption, food efficiency rate, mortality or behavioural reactions of the F0, F1 and F2 parents. No effects at any dose level or generation on reproductive or fertility parameters, population data, survival, growth, behaviour or histopathological findings. The NOEL for general and reproductive/ developmental toxicity was 500 ppm MCPA-thioethyl, equivalent to 25 mg/kg bw/day. **The NOEL for systemic and reproductive/ developmental toxicity was at least 500 pm, approximately equivalent to 25 mg/kg bw/day.**	Morgan, 1976*
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, 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	**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 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.	Mackenzie, 1986*

sex/ group. Tissues examined in all control and high dose F0 and F1b adults.		
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	Irvine, 1980a (Preliminary dose range finding study Irvine &

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.	teratogenic nor embryotoxic.	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	This applicant does not have access to the study report or data. However, the results are considered to be	Roll & Mattiaschk, 1983

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 Oral gavage (gestation days 6-15) Termination day 18. Foetuses examined for external, visceral and skeletal abnormalities.	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 • 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 to be unreliable.**	(Publication)

* Key studies for consideration of MCPA-thioethyl classification

4.11.1 Effects on fertility

4.11.1.1 Non-human information

Three studies have been conducted in the rat to evaluate potential effects on fertility and reproduction outcomes. For MCPA-thioethyl a three generation, 2 litters/generation study has been conducted (Morgan, 1976). This is an old, pre-GLP study which nevertheless provides reliable information for inclusion here. A more recent and GLP compliant study of MCPA has been conducted which includes two generations and 2 litters/generation (Mackenzie, 1986). A concurrent one-generation study has been conducted for MCPA (Milburn, 2004a). Collectively, these studies are considered to provide a good and reliable database for evaluation of potential adverse effects on reproductive toxicity.

In the non-GLP study reproduction study (Morgan, 1976) groups of 10 male and 20 female Charles River albino rats received MCPA-thioethyl in the diet at 0, 20, 100 or 500 ppm continuously over 3 generations. Doses of up to and including 500 ppm had no effect on the growth, food consumption, food efficiency rate, incidence of mortality or clinical/behavioural reactions of the F0, F1 or F2 parents. Necropsy of the parent animals and histopathological examination of the organs revealed no evidence of any treatment-related effects at any dose up to and including 500 ppm. There were no treatment-related effects on any of the reproductive or fertility parameters, population data, pup survival, growth, behaviour or histopathological findings in the progeny of the 3 generations evaluated. Under the conditions of this study, which was not conducted to current test guideline requirements, the NOEL for general and reproductive/ developmental toxicity was 500 ppm MCPA-thioethyl, approximately equivalent to 25 mg/kg bw/day (Morgan, 1976).

The effects of MCPA on the reproduction and postnatal development of Sprague-Dawley rats were investigated in a two-generation (two litters per generation) study which was conducted to GLP and regulatory test guidelines (Mackenzie, 1986). MCPA was administered continuously in the diet at

dose levels of 0, 50, 150 or 450 ppm (equivalent to approx. 4, 12 and 40 mg/kg bw/day, respectively). NB. These equivalents are taken from JMPR. They differ from the DAR. The DAR values are more in line with the Morgan study but JMPR has a table of achieved dose. There were no treatment-related deaths or clinical signs. At 450 ppm there was a significant reduction of body weight from weaning through the premating period in the F1b adults of both sexes. Pup body weight gain at 450 ppm was marginally reduced in the F1a and F1b and significantly reduced in the F2a and F2b. There was no treatment-related effect on reproduction or litter parameters or on the incidence of gross or histopathological abnormalities. The NOAEL for reproductive toxicity was 450 ppm (approximately equal to 22 mg/kg bw/day). The NOAEL for parental toxicity was 150 ppm (approximately equal to 8 mg/kg bw/day). The NOAEL for pup toxicity was also 150 ppm based on reduced body weight gain pre-weaning at 450 ppm.

A one-generation reproduction study was conducted using Alpk:APfSD (Wistar-derived) rats (12/sex/group) and fed diets containing MCPA at concentrations of 0, 450, 750 or 1000 ppm (Milburn, 2004). The purpose of the study was to clarify the dose–response relationship in rat pups compared with adults and hence the achieved dose was determined accurately. 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 deaths or clinical signs. 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. There was no treatment-related effect on reproduction or litter parameters. Absolute liver, ovary and testes weights were approximately 10% below control values in high-dose F1 males and females but when adjusted for body weight, there was no difference from controls.

The NOAEL of MCPA for reproductive toxicity was 1000 ppm (approximately equal to 88 mg/kg bw/day), the highest dose tested. The NOAEL for parental toxicity was less than 450 ppm (approx. 38 mg/kg bw/day) based on lower body weight. The NOAEL for pup toxicity was 750 ppm (approx. 114 mg/kg bw/day), based on reduced body weight at the highest dose of 1000 ppm (approx. 1560 mg/kg bw/day).

The results of the three studies in terms of no effect levels is summarised in the following table.

Table 19: Summary of reproductive study outcomes

Study	Reproductive toxicity	Parental toxicity	Pup toxicity
MCPA-thioethyl 0, 20, 100, 500 ppm 3 Generation study (Morgan, 1976)	NOAEL 500 ppm (25 mg/kg bw/day)	NOAEL 500 ppm (25 mg/kg bw/day)	NOAEL 500 ppm (25 mg/kg bw/day)
MCPA 0, 50, 150 or 450 ppm 2 Generation study (Mackenzie, 1986)	NOAEL 450 ppm (40 mg/kg bw/day)	NOAEL 150 ppm (12 mg/kg bw/day)	NOAEL 150 ppm (12 mg/kg bw/day)
MCPA 1 Generation study 0, 450, 750, 1000 ppm (Milburn, 2004)	NOAEL 1000 ppm (88 mg/kg bw/day)	NOAEL < 450 ppm (38 mg/kg bw/day)	NOAEL 750 ppm (114 mg/kg bw/day)

(mg/kg/day values are approximate)

No adverse effects on fertility or reproduction were observed at any dose level evaluated.

4.11.1.2 Human information

No relevant information.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Investigations of prenatal developmental toxicity have been conducted in the rat, rabbit and mouse.

Rat

The studies of developmental toxicity in the rat have been conducted on MCPA-thioethyl (Tauchi, 1984) and MCPA (Hellwig & Hilderbrand, 1993a) and Irvine (1980a).

In the GLP study of MCPA-thioethyl (Tauchi, 1984), groups of 23 inseminated SPF Wistar Imamichi rats, were dosed daily by gavage with 0, 10, 40 or 160 mg/kg bw from day 6-15 of gestation. The dose levels were based on the results of a preliminary study which investigated 4, 16, 64, 128 and 256 mg/kg bw/day in groups of 7 rats dosed on gestation days 6 to 15 inclusive. The highest dose level of 256 mg/kg bw/day induced severe maternal toxicity and increased foetal mortality. As 128 mg/kg bw/day did not adversely affect maternal animals, 160 mg/kg bw/day was selected as the highest dose for the developmental toxicity.

All doses were suspended in 0.5% aqueous sodium carboxymethylcellulose solution. Maternal toxicity was evident at 160 mg/kg bw/day with reduced body weight gain and food intake, increased water intake and increased spleen weight. At this dose, foetuses showed reduced body weight and reduced ossification of the sacral and caudal vertebrae. There were no external, visceral or skeletal malformations attributable to MCPA-thioethyl administration. The NOEL for both maternal and developmental toxicity was 40 mg/kg bw/day (Tauchi, 1984).

In a GLP study of MCPA acid (Hellwig & Hildebrand, 1993a), groups of 22 - 24 mated female Wistar rats were dosed daily by gavage with 0, 15, 60 or 120 mg/kg bw from day 6-15 of gestation. The dose

levels were based on the results of a preliminary study (Hellwig, 1992a) which investigated 80, 120 and 160 mg/kg bw/day in groups of 10 rats dosed on gestation days 6 to 15 inclusive. The highest dose level of 160 mg/kg bw/day induced maternal toxicity and decreased foetal body weight but no treatment-related foetal abnormalities. The dose of 120 mg/kg bw/day was selected as the highest dose for the developmental toxicity.

All doses were suspended in 0.5% aqueous carboxymethylcellulose solution. At 120 mg/kg bw/day, 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/day.

At 120 mg/kg bw/day, 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. The NOEL for maternal and developmental toxicity was 60 mg/kg bw/day (Hellwig and Hildebrand, 1993a).

In a preliminary, pre-GLP study of MCPA (Irvine & Tucker, 1978a), mated female Sprague Dawley rats were dosed daily by gavage with 0, 25 or 100 mg/kg bw from day 0-20 of gestation. All doses were suspended in 1% methylcellulose solution. At both dose levels, the body weight gain was slightly retarded without a clear dose-related pattern. Reduced foetal body weight and crown-rump length were observed at 100 mg/kg bw/day. This study was followed by a non-GLP teratogenicity study of MCPA (Irvine, 1980a) comprising groups of 5 mated female Sprague Dawley rats dosed daily by gavage with 0, 20, 50 or 125 mg/kg bw from day 6-15 of gestation. No maternal or developmental effects were observed at any dose level. No definitive conclusions can be drawn from these two studies (Irvine & Tucker, 1978a and Irvine, 1980a) due to the small number of animals used and the inconsistent periods of exposure but, they do not indicate any teratogenicity to MCPA.

Evaluations of prenatal developmental toxicity in the rat, indicate that neither MCPA-thioethyl nor MCPA acid induce teratogenicity. Developmental toxicity manifest as reduced foetal body weight and reduced skeletal ossification was observed only in the presence of maternal toxicity. The NOEL for maternal and developmental toxicity in the rat was 40 mg/kg bw/day for MCPA-thioethyl and 60 mg/kg bw/day for MCPA.

Rabbit

The studies of developmental toxicity in the rabbit have been conducted on MCPA-thioethyl (Sakamaki, 1985) and MCPA (Hellwig & Hildebrand, 1993b) and Irvine (1980b).

In the GLP study of MCPA-thioethyl (Sakamaki, 1985), groups of 16 mated female Japanese white rabbits, were dosed daily by gavage with 0, 40, 80 or 160 mg/kg bw from day 6-18 of gestation inclusive. The dose levels were based on the results of a preliminary study which investigated 50, 100 and 200 mg/kg bw/day in groups of 2-3 pregnant rabbits dosed on gestation days 6 to 18 inclusive. One of two rabbits given 200 mg/kg bw/day died on gestation day 21 following reduced food and water intake and suppression of body weight. In the other dose groups, no changes were observed in the dams or foetuses. The highest dose level of 160 mg/kg bw/day was selected as the highest dose for the developmental toxicity with reference also to the rat developmental study (Tauchi, 1984).

All doses were suspended in 0.5% sodium carboxymethylcellulose solution. Death following abortion occurred in one rabbit in each of the 80 and 160 mg/kg bw/day groups. However, there was no change in body weight, food intake, organ weights (heart, liver, spleen, kidney, adrenal and ovary) or the incidence of macroscopic findings at necropsy. There were no developmental effects and no malformation at any dose level of MCPA-thioethyl. The NOEL for maternal toxicity was considered to be 40 mg/kg bw/day and the NOEL for developmental toxicity 160 mg/kg bw/day (Sakamaki, 1985).

In a GLP study of MCPA acid (Hellwig & Hildebrand, 1993b), groups of 15 mated female Himalayan rabbits (Chbb:HM outbred strain) were dosed daily by gavage with 0, 15, 30 or 60 mg/kg bw from day 7-19 of gestation inclusive. The dose levels were based on the results of a preliminary study (Hellwig, 1992b) which investigated 50, 75 and 100 mg/kg bw/day in groups of 5 rabbits dosed on gestation days 7 to 19 inclusive. Death preceded by a general decline in health was observed at 75 and 100 mg/kg bw/day. Post-implantation losses were elevated at 75 and 100 mg/kg bw/day but within the historical control range. There were no treatment-related foetal abnormalities. The dose of 60 mg/kg bw/day was selected as the highest dose for the developmental toxicity.

All doses were suspended in 0.5% aqueous carboxymethylcellulose solution. At 60 mg/kg bw/day, one dam died on day 20 and another was sacrificed in a moribund condition on day 21. Both dams had exhibited piloerection and no defecation). Ulcerations of the stomach mucosa were found in both decedents. At 30 mg/kg bw/day, one dam aborted on day 21 and was terminated. Focal haemorrhagic oedema of the colon was observed a t necropsy. At 60 mg/kg bw/day, a small but not significant overall loss of maternal body weight was observed together with reduced feed consumption. There was no indication of embryo / foetal toxicity or teratogenicity at any dose. The NOEL for maternal toxicity was 15 mg/kg bw/day and the NOEL for developmental toxicity was 60 mg/kg bw day (Hellwig and Hildebrand, 1993b).

In a preliminary, pre-GLP study of MCPA (Irvine & Tucker, 1978b), mated female Dutch Belted rabbits were dosed daily by gavage with 0, 25 or 100 mg/kg bw from day 1-27 of gestation. All doses were suspended in 1% carboxymethylcellulose solution. At 100 mg/kg bw/day, one rabbit died on day 10, preceded by ataxia and body weight loss. Ataxia was observed in another high-dose rabbit that survived to scheduled termination. There were no treatment-related findings at 25 mg/kg bw/day. Pregnancy was low across all groups (6/10, 2/5 and 3/5 at 0, 25 and 100 mg/kg bw/day, respectively). All fetuses died in utero at 100 mg/kg bw/day although prenatal mortality was also high at 0 and 25 mg/kg bw/day. There were no treatment-related foetal malformations or variations observed at 25 mg/kg bw per day. Fetal weight and crown-rump length were decreased at 25 mg/kg bw/day.

This study was followed by a non-GLP teratogenicity study of MCPA (Irvine, 1980b) comprising groups of 15-18 mated female rabbits dosed daily by gavage with 0, 5, 12, 30 or 75 mg/kg bw from day 6-18 of gestation. Deaths were observed at and above 12 mg/kg bw/day and were considered to have occurred 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 NOEL for maternal toxicity was considered to be 5 mg/kg bw/day and the NOEL for developmental toxicity 30 mg/kg bw/day. However, the possible confounding effect of respiratory infection on the study outcomes makes the conclusions on NOEL's unreliable.

Evaluations of prenatal developmental toxicity in the rabbit, indicate that neither MCPA-thioethyl nor MCPA acid induce teratogenicity. The NOEL of MCPA-thioethyl for maternal toxicity in the rabbit was 40 mg/kg bw/day and the NOEL for developmental toxicity was 160 mg/kg bw/day. The NOEL of MCPA for maternal toxicity in the rabbit was 15 mg/kg bw/day and the NOEL for developmental toxicity was 60 mg/kg bw/day.

Mouse

A study of the developmental toxicity of MCPA in the mouse has been published (Roll & Mattiaschk, 1983). The report and data are not available to the applicant for assessment and the quality of the study is unknown. The DAR for MCPA, MCPA-thioethyl reports that the results should be considered with caution because the strain of mouse used has a high background incidence of cleft palate. The lack of reported data is also noted.

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 MCPA was dissolved in peanut oil for dosing. The dams showed a dose-dependent reduction in body weight gain at ≥ 200 mg/kg bw/day. Other signs of maternal toxicity such as clinical signs and mortality were reported with insufficient detail. An increase in post-implantation loss occurred at ≥ 300 mg/kg bw/day. Foetal body weight was reduced at > 100 mg/kg bw/day in a dose-related pattern. An increased incidence of malformation including cleft palate and fused ribs was dose-related at ≥ 200 mg/kg bw/day. It was concluded that the NOEL for maternal toxicity was100 mg/kg bw/day and the NOEL for developmental toxicity was 50 mg/kg bw/day.

The authors noted that the oral LD_{50} of MCPA in mice is 600 mg/kg bw; this is not confirmed in the DAR or in the JMPR 2012 Monograph and cannot be confirmed. If correct, some of the selected dose levels for the developmental toxicity study would have been in the range of the cited LD_{50} value. As key information on maternal mortality and clinical condition were not reported in the paper, the extent of the maternal effects cannot be determined. The authors also considered it possible that at clearly maternally toxic doses, MCPA could elicit unspecific teratogenic effects consisting mainly of cleft palates. The NMRI strain has a high background incidence of cleft palate, indicating an enhanced susceptibility to this kind of malformation.

The quality of this publication (Roll & Mattiaschk, 1983) on the evaluation of the developmental toxicity of MCPA in the mouse is unknown and the suitability of the dosing regimen and selected animal model are questionable. For these reasons, the reported outcomes cannot be considered credible or relevant to the evaluation of the potential effects of MCPA on foetal development.

4.11.2.2 Human information

No relevant information.

4.11.3 Other relevant information

No further relevant information.

4.11.4 Summary and discussion of reproductive toxicity

Investigations of the potential for MCPA-thioethyl and MCPA to impair fertility and reproductive performance or to adversely affect the outcome of pregnancy and postnatal growth of the offspring include a three generation and a two generation study (both with 2 litters per generation) and a one generation study. No reproductive toxicity was observed in any study and the highest NOAEL of 88 mg/kg bw/day is determined from a one generation study of MCPA (Milburn, 2004). No adverse effects due to MCPA-thioethyl or MCPA were observed in relation to the number of pups born or their viability. Lower pup body weights when seen occurred towards the end of the lactation period and in relation to direct consumption of the diet. The highest NOAEL for systemic toxicity is 38 mg/kg bw/day determined from the one generation study of MCPA (Milburn, 2004).

GLP investigations of the potential for MCPA-thioethyl and MCPA to induce prenatal developmental toxicity have been conducted in the rat and rabbit. Neither MCPA-thioethyl nor MCPA induced foetal malformation in either species. In the rat, reduced foetal body weight and reduced skeletal ossification were observed only in the presence of maternal toxicity. The NOEL for maternal and developmental toxicity in the rat was 40 mg/kg bw/day for MCPA-thioethyl and 60 mg/kg bw/day for MCPA. In the rabbit, no developmental toxicity was observed at the highest dose levels tested. The NOEL of MCPA-thioethyl for maternal toxicity in the rabbit was 40 mg/kg bw/day and the NOEL for developmental toxicity was 160 mg/kg bw/day. The NOEL of MCPA for maternal toxicity in the rabbit was 15 mg/kg bw/day and the NOEL for developmental toxicity was 60 mg/kg bw/day.

4.11.5 Comparison with criteria

The criteria for classification are as follows:

Category 1A: Known human reproductive toxicant: is largely based on evidence from humans.

Category 1B: Presumed human reproductive toxicant: is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Category 2: Suspected human reproductive toxicant: Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.

Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

Neither MCPA-thioethyl nor MCPA was found to induce any adverse effect on fertility, reproduction, pregnancy outcome or littering in the rat. Three studies have been conducted and include one, two and three generation reproduction studies.

Neither MCPA-thioethyl nor MCPA induced foetal malformation in rats or rabbits. In the rat, the developmental effects of reduced foetal body weight and reduced skeletal ossification were observed only in the presence of maternal toxicity. In the rabbit, no developmental effects were observed at maternally toxic doses.

MCPA-thioethyl does not meet the criteria for classification as a reproductive toxicant.

4.11.6 Conclusions on classification and labelling

CLP: No classification

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Table 20: Summary table of relevant neurotoxicity studies

<table>
<tr><th>Method</th><th>Results and Remarks</th><th>Reference</th></tr>
<tr><td>Acute
Rat: (Chbb:THOM (SPF)
10/sex/group
Single oral dose by gavage
Guideline: not stated
GLP: not stated
Test Material: MCPA (Purity: IUCLID technical dossier)
0, 200, 400 or 800 mg/kg bw/day for males; 0, 150, 300 or 600 mg/kg bw/day for females.
Vehicle: 0.5% aqueous CMC
Rats observed for 2 weeks, detailed functional observational battery and motor activity assessment.
Neurological tissues examined histopathologically.</td><td>There were no deaths.
800 mg/kg bw/day (M): body weights 9% and 5% lower than the control on days 7 and 14, respectively. Body weight gain to day 7 and day 14 was approximately 48% and 12% lower than the control values, respectively.
400 mg/kg bw/day (M): body weight gain was 12% lower than the control value to day 7.

Incidence of clinical signs at 24 hours: (n=10)
<table>
<tr><th>Males/ mg/kg/day</th><th>0</th><th>200</th><th>400</th><th>800</th></tr>
<tr><td>Hypo-activity</td><td>0</td><td>0</td><td>1</td><td>4</td></tr>
<tr><td>↓ arousal</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Ataxia</td><td>0</td><td>0</td><td>3</td><td>10</td></tr>
<tr><td>Rearing (mean)</td><td>3.7</td><td>3.6</td><td>2.5</td><td>0.8**</td></tr>
<tr><td>↑ abdominal tension</td><td>0</td><td>0</td><td>2</td><td>8</td></tr>
<tr><td>↓righting response</td><td>0</td><td>0</td><td>0</td><td>7</td></tr>
<tr><td>Overall motor activity[a]</td><td>173</td><td>161</td><td>113</td><td>65***</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><th>Females/ mg/kg/day</th><th>0</th><th>150</th><th>300</th><th>600</th></tr>
<tr><td>Hypo-activity</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>↓ arousal</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Ataxia</td><td>0</td><td>0</td><td>0</td><td>10</td></tr>
<tr><td>Rearing (mean)</td><td>7.8</td><td>6.2</td><td>6.3</td><td>3.8</td></tr>
<tr><td>↑ abdominal tension</td><td>0</td><td>0</td><td>4</td><td>10</td></tr>
<tr><td>↓righting response</td><td>0</td><td>0</td><td>0</td><td>5</td></tr>
<tr><td>Overall motor activity[a]</td><td>220</td><td>198</td><td>226</td><td>121***</td></tr>
</table>
** p< 0.01 *** p< 0.02
[a] interruptions per rat per interval.

Ataxia and ↑ abdominal tension at the middle and high doses; ↓activity, ↓ rearing and ↓righting response at the highest dose. At the highest dose, motor activity was impaired in both sexes 24 hours after dosing, but not on day 7 or 14. Histopathological examinations detected no treatment-related effect on the nervous system. The clinical signs observed during the functional observational battery are attributed to acute systemic toxicity, rather than to a direct neurotoxic effect.
The NOAEL was 150 mg/kg bw.</td><td>Mellert et al , 1994a *</td></tr>
</table>

Subacute Rat: (Chbb:THOM (SPF) 15/sex/group Dietary for 90 days Guideline: not stated GLP: not stated Test Material: MCPA (Purity: IUCLID technical dossier) 0, 50, 500 or 2500 ppm (equivalent to 0, 3, 34 and 177 mg/kg/day for males and 0, 4, 42 and 188 mg/kg bw/day for females Functional observational battery and motor activity assessment on 10 rats / sex/ group prior to dosing and during weeks 4, 8 and 13. Blood and urine taken at termination. Neurological tissues on 5/sex/group examined histo-pathologically.	**2500 ppm (177 mg/kg bw/day):** bodyweights decreased by 27 -21% for males and females, respectively and body weight gain reduced by 42 and 48%. Food consumption also significantly reduced. Decreased forelimb grip in males on day 50, decreased hind limb grip strength in females at day 85 and decreased landing foot splay on day 22. Motor activity was slightly reduced for both males and females on days 22, 50 and 85. Haematological changes in red cell parameters consistent with macrocytic anaemia. Reductions in white cell counts in females and reduced leucocyte count in females. Prolonged prothrombin times in females. Srum glucose, total protein and globulins and increased urea, creatinine and enzyme activity. Serum triglycerides significantly reduced for both sexes. Absolute liver weight increased for females. Relative kidney weight significantly increased for males. Lower relative adrenal weights (females) and testes weights could not be attributed to the lower body weights. Pathology showed marked hepatocellular cytoplasmic eosinophilia and granular cytoplasm. Minimal to moderate foam cells in the lung of males and females. A number of animals showed hypercellularity of the bone marrow, consistent with impaired red cell production Increased lipid in adrenals. Diffuse atrophy of the testes (severe to extreme) in all males with oligozoospermia and aspermia in 3 and 7 rats, respectively. Thymic atrophy occurred in 3 females. No treatment-related neurohistopathology. **500 ppm (34 mg/kg bw/day):** bodyweight gain reduced by 12% at week 13. Serum triglycerides for males significantly reduced compared to controls. Relative kidney weight significantly increased for males, associated with increase urea and creatinine levels, but no pathology correlate. Lower relative adrenal weights (females) and testes weights could not be attributed to the lower body weights. Increased lipid in adrenals. **50 ppm (3 mg/kg bw/day):** No adverse effects. **The NOAEL was 50 ppm (3 mg/kg bw/day) based on reduced bodyweight gain in females, increased relative kidney weight in males and increased adrenal lipid at 500 ppm (34 mg/kg bw/day).**	Mellert et al, 1994b *

* Key studies for consideration of MCPA-thioethyl classification

Acute Neurotoxicity

MCPA in 0.5% w/v aqueous carboxymethylcellulose was administered by gavage as a single dose to groups of 10 Wistar rats (Chbb:THOM (SPF) strain) of each sex at 0, 200, 400 or 800 mg/kg bw for males and at 0, 150, 300 or 600 mg/kg bw for females and observed for 2 weeks. Rats were observed daily for clinical signs, with a more detailed examination performed weekly. Body weight was recorded weekly. A functional observational battery and motor activity assessment were performed on all rats 7 days prior to dosing and at 24 hours, 2 days and 14 days after dosing. Survivors were sacrificed after 14 days, and tissues from five rats of each sex per group were prepared for neuropathological examinations. There were no deaths. Mean absolute body weight of high-dose

males was approximately 9% and 5% lower than the control values on days 7 and 14, respectively. Body weight gain to day 7 and day 14 was approximately 48% and 12% than the control values, respectively, in high-dose males. The mean body weight gain of mid-dose males was approximately 12% lower than the control value to day 7. Although a similar pattern of lower body weight and body weight gain occurred in high-dose females, albeit of a smaller magnitude (approximately 3% and 20% lower than the control value, respectively), there was no significant difference relative to the control. Clinical signs were observed only during the functional observational battery performed 24 hours after dosing. Ataxia and increased abdominal tension were observed at the middle and high doses, whereas impaired activity, reduced rearing and decreased righting response occurred at the highest dose. At the highest dose, motor activity was impaired in both sexes 24 hours after dosing, but not on day 7 or 14. Histopathological examinations detected no treatment-related effect on the nervous system. On this basis, the clinical signs observed during the functional observational battery are attributed to acute systemic toxicity, rather than to a direct neurotoxic effect. The NOAEL was 150 mg/kg bw, based on the occurrence of clinical signs observed during the functional observational battery and impaired motor activity at 300 mg/kg bw.

Sub-acute Neurotoxicity

MCPA was administered to groups of 15 Wistar rats (Chbb: THOM (SPF) strain) of each sex for 3 months at a dietary concentration of 0, 50, 500 or 2500 ppm (equal to 0, 4, 38and 183 mg/kg bw/day, respectively). Achieved doses were 0, 3, 34 and 177 mg/kg bw/day for males and 0, 4, 42 and 188 mg/kg bw/day for females at 0, 50, 500 and 2500 ppm, respectively. The study incorporated all the elements of a guideline sub-chronic toxicity study. Rats were observed daily for clinical signs, with body weight and feed consumption recorded weekly. A functional observational battery and motor activity assessment were performed on 10 rats of each sex per dose prior to the commencement of dosing and during weeks 4, 8 and 13. Blood and urine were collected from 10 rats of each sex per group at the end of the study for the analysis of standard haematology, clinical chemistry or urine analysis parameters. Ophthalmoscopy was performed on 10 rats of each sex per group at the end of the study. Following scheduled sacrifice, tissues were prepared from five rats of each sex per group for neuropathological examination. Remaining rats were macroscopically examined; organs were weighed and examined histopathologically. One high-dose female died on day 57 due to cachexia. The only treatment-related clinical sign observed during general daily observations was paleness in 1 male and in 13 females at the highest dose. At the highest dose, absolute body weight was approximately 27% and 21% lower than the control values in high-dose males and females, respectively, whereas overall body weight gain was approximately 42% and 48% lower than the control values, respectively. In mid-dose females, body weight gain to day 90 was approximately 12% lower than the control value. Feed consumption was decreased at the highest dose (approximately 15–33% lower than the control value in males and approximately 18–38% lower in females). Water consumption was increased in mid-dose females (approximately 13–41% higher than the control value) and at the high dose (approximately 22–42% higher than the control value in males and approximately 87–145% higher than the control value in females). Treatment-related functional observational battery findings were confined to the highest dose and included paleness (two males and five females on day 85), decreased forelimb grip strength in high-dose males on day 50 (4.2 N versus 4.8 N in the control), decreased hind limb grip strength in females on day 85 (1.6 N versus 2.2 N) and decreased landing foot spread in males on day 22 (11 cm versus 12.5 cm in the controls). Motor activity was approximately 20–30% lower than the control values in high-dose males and females on days 22, 50 and 85, but the changes did not attain statistical significance. Changes in red cell parameters consistent with macrocytic anaemia occurred at the highest dose (reduced erythrocytes, haemoglobin, haematocrit and mean corpuscular haemoglobin concentration). Significantly decreased white blood cell counts occurred in high-dose females; in the males, there was a trend towards reduced leukocyte numbers. In high-dose females, significantly prolonged

prothrombin times were noted. Effects on clinical chemistry parameters occurred mainly at the highest dose and included significantly reduced glucose, total proteins and globulins and increased urea, creatinine, ALT, AST and ALP activities. Serum triglyceride concentrations were significantly lower than the control values at the middle (males) and high doses (both sexes). In high-dose females, urine volume was increased and urine specific gravity significantly decreased. The increase in absolute liver weight in high-dose females occurred in conjunction with elevated serum enzymes and histopathology and is therefore considered treatment related. The relative kidney weights of mid- and high-dose males were significantly increased relative to the control values, with the increase in 500 ppm males not attributable to the lower body weight. This may correlate with disturbances of creatinine and urea seen in males, although no histological abnormalities in the kidneys were detected. Lower relative adrenal weights (females) and testes weights (in males) also cannot be attributed to lower body weight. Gross pathological findings occurred mainly at the highest dose and included the following prominent acinar pattern of the liver, dilatation of the heart, reduced size of kidney, testes, epididymides, and seminal vesicle; and discoloration of the adrenal cortex. Histopathology revealed marked hepatocellular cytoplasmic eosinophilia and granular cytoplasm (moderate or severe) in the liver of all high-dose males and nine high-dose females. Single cases of anisokaryosis and increased mitosis (slight) were observed in the liver of high-dose males. Bile duct hyperplasia (minimal) occurred in two high-dose males. Foam cells (minimal to moderate) were detected in the lungs of mid- and high-dose males (one and eight rats, respectively, versus zero in the controls) and high-dose females (nine versus zero in the controls). Hypocellularity of the bone marrow (slight or moderate) (five high-dose females) and hypocellularity of the marrow from the cervical (three high-dose females), thoracic (three high-dose females) and lumbar cord (three high-dose females) and sternum (six high-dose males and six high-dose females, minimal to severe) were consistent with the perturbations in haematological parameters, suggesting impaired red cell production. Increased lipid storage in the adrenal cortex (minimal to severe) was the only histological finding in this tissue, despite markedly lower adrenal weights (1/10, 0/10, 7/10 and 10/10 males and 1/10, 0/10, 6/10 and 9/10 females at 0, 50, 500 and 2500 ppm, respectively). Diffuse atrophy of the testes (graded as severe or extreme) occurred in all high-dose males. Oligozoospermia and aspermia (extreme) were detected in the epididymis at the highest dose (three and seven rats, respectively). Thymic atrophy (moderate or severe) occurred in three high-dose females. There were no treatment-related neuropathological findings.

The NOAEL was 50 ppm (equal to 3 mg/kg bw per day), based on reduced body weight gain in females, increased relative kidney weight in males and increased adrenal lipid in both sexes at 500 ppm (approximately equal to 34 mg/kg bw per day) (Mellert et al, 1994b).

4.12.1.2 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.

4.12.1.3 Specific investigations: other studies

Haematology

A number of studies have been published to investigate *in vitro* effects of MCPA on platelets and erythrocytes (Elo et al, 1991, Bukowska et al, 2000, Duchnowicz et al, 2002). These studies are considered to have no direct relevance to the CLP classification for MCPA-thioethyl.

Enzyme induction and peroxisome proliferation

A number of studies have been published to investigate hepatic enzyme induction and peroxisome proliferation (Hietanen et al., 1983; Ahotupa et al, 1983; Mustonen et al, 1989; Inomata et al, 1991a and 1991b; Maloney and Waxman, 1999). As MCPA-thioethyl and MCPA do not warrant classification for carcinogenicity, these studies do not need to be considered in this document.

4.12.1.4 Human information

No further data.

4.12.2 Summary and discussion

There was no evidence in the available studies that MCPA-thioethyl has neurotoxicity or immunotoxicity potential. As the results of these studies impact on the interpretation of specific target organ toxicity following single (STOT SE) or repeat exposure (STOT RE) and/or carcinogenicity the results of these studies were also considered previously.

4.12.3 Comparison with criteria

There was no indication that MCPA-thioethyl is neurotoxic or immunotoxic.

4.12.4 Conclusions on classification and labelling

No classification for neurotoxicity, immunotoxicity or carcinogenicity.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 21: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Aqueous hydrolysis OECD Guideline 111 (Hydrolysis as a Function of pH) EPA OPPTS 835.2110 (Hydrolysis as a Function of pH) OECD 111 Proposal for revision of guideline OECD 111: Hydrolysis as a function of pH. Draft document, August 2001.	Half-life (DT_{50}): t1/2 (pH 4): 23.5 d at 20°C; Rate constant: 0.02951 d-1; Type: (pseudo-)first order (= DT_{50}) (r2=0.981, DT90=78 days) t1/2 (pH 7): 12.5 d at 20°C; Rate constant: 0.05523 d-1;	MCPA-thioethyl - Analytical purity: 92 % [ring-U-14C]-Phenothiol - Analytical purity: 99.0% (HPLC),	Slangen PJ. 2002 KCA 7.2.1.1/01

Method	Results	Remarks	Reference
	Type: (pseudo-)first order (= DT_{50}) (r2=0.989, DT_{90}=41.7 days) t1/2 (pH 9): 0.45 at 20°C; Rate constant: 1.53414 ; Type: (pseudo-)first order (= DT_{50}) (r2=0.997, DT_{90}=1.5 days) Transformation products: yes (MCPA)	98.2% (Radio-GC), 98.1% (TLC) Klimisch 1 (reliable without restriction)	
OECD Guideline 111 (Hydrolysis as a Function of pH) EPA OPPTS 835.2110 (Hydrolysis as a Function of pH)	Half-life (DT_{50}): t1/2 (pH 4): 26.5 d at 20 °C; Rate constant: 0.026 d-1; Type: (pseudo-)first order (= DT_{50}) (r2 = 0.904; DT_{90} = 99.2d) t1/2 (pH 7): 7.4 d at 20 °C; Rate constant: 0.094 d-1; Type: (pseudo-)first order (= DT_{50}) (r2 = 0.959; DT_{90} = 24.5d) Recovery (in %): pH 4: 101 at 20 °C after 0 d pH 4: 89.5 at 20 °C after 31 d pH 7: 100 at 20 °C after 0 d pH 7: 95 at 20 °C after 31 d Transformation products: yes	MCPA-thioethyl - Analytical purity: 92% [ring-U-14C]-Phenothiol - Analytical purity: 99.0% (HPLC), 98.2% (Radio-GC), 98.1% (TLC) Klimisch 1 (reliable without restriction)	Wonders J, Slangen PJ & van Noorloos B. (2002) KCA 7.2.1.1/02
Study type: direct photolysis OECD Guideline draft (Phototransformation of Chemicals in Water - Direct and Indirect Photolysis) EPA Guideline Subdivision N 161-2 (Photodegradation Studies in Water) EPA OPPTS 835.2210 (Direct Photolysis Rate in Water by Sunlight) Calculations were performed with ModelManager v 1.1; simple first order (SFO) degradation kinetics were assumed. Light source: Xenon lamp Light spectrum: 300 — 800	Half-life (DT_{50}): t1/2: 0.63 d (Irradiated) t1/2: 4.38 d (Dark control) % Degradation: 88.79 after 2.2 d (Irradiated) 38.9 after 2.2 d (Dark control) Quantum yield: 0.0107 Transformation products: yes	MCPA-thioethyl - Analytical purity: 92% [ring-U-14C]-Phenothiol - Analytical purity: 99.0% (HPLC), 98.2% (Radio-GC), 98.1% (TLC) Klimisch 1 (reliable without restriction)	Willems H. (2003) KCA 7.2.1.2/01
Study type: direct photolysis OECD Guideline draft (Phototransformation of Chemicals in Water - Direct and Indirect Photolysis)	Spectrum of substance: At the study concentration, the absorbance at 295nm was 0.0014 (OECD guideline states <0.02 therefore OK) Half-life (DT_{50}):	MCPA-thioethyl technical - Analytical purity: 97.3% [14C]-MCPA-thioethyl -	Haynes LM (2015a) KCA 7.2.1.2/02

Method	Results	Remarks	Reference
The determination of the kinetic values followed the recommendations of FOCUS rules and guidelines and was aimed at investigating potential exceedance of trigger values according to the FOCUS guidance document on degradation kinetics. A simple first order kinetic model was selected as the best-fit kinetic model for the data. Light source: Xenon lamp Light spectrum: 250 — 800 Rel. light intensity: 1.97	t1/2: 20.6 h (Irradiated buffered water at pH 7 under continuous Suntest irradiation) t1/2: 1.69 d (equivalent summer sunlight at 40ºN) % Degradation: 66.9 after 40 h (Irradiated) Quantum yield: 0.00337 Transformation products: yes	Analytical purity: 99.4 % Klimisch 1 (reliable without restriction)	
Study type: indirect photolysis OECD Guideline draft (Phototransformation of Chemicals in Water - Direct and Indirect Photolysis) The determination of the kinetic values followed the recommendations of FOCUS rules and guidelines and was aimed at investigating potential exceedance of trigger values according to the FOCUS guidance document on degradation kinetics. A simple first order kinetic model was selected as the best-fit kinetic model for the data. Light source: Xenon lamp Light spectrum: 250 — 800 Sensitiser: natural water	Spectrum of substance: At the study concentration, the absorbance at 295nm was 0.0012 (OECD guideline states <0.02 therefore OK) Half-life (DT_{50}): t1/2: 18.1 h (Irradiated sterile natural water under continuous Suntest irradiation) t1/2: 1.61 d (equivalent summer sunlight at 40ºN) % Degradation: 84.2 after 40 h (Irradiated) Rate constant: 0.03833 hr^{-1} Transformation products: yes	MCPA-thioethyl technical - Analytical purity: 97.3% [14C]-MCPA-thioethyl - Analytical purity: 99.4 % Klimisch 1 (reliable without restriction)	Haynes LM (2015b) KCA 7.2.1.3/01
Test type: ready biodegradability activated sludge, domestic (adaptation not specified) OECD Guideline 301 B (Ready Biodegradability: CO_2 Evolution Test)	Not readily biodegradable % Degradation of test substance: 53.6 % after 28 d (CO_2 evolution)	MCPA-thioethyl technical - Analytical purity: 97.3% Klimisch 1 (reliable without restriction)	Brunswik-Titze A (2015) KCA 7.2.2.1/01
Test system: natural water OECD Guideline 309 (Aerobic Mineralisation in Surface Water - Simulation Biodegradation Test)	Half-life (DT_{50}): 0.73 h in water at 20 °C (Initial concentration: 10 µg/L) 1.1 h in water at 20 °C (Initial concentration: 100 µg/L) % Degradation of test substance: after 0.5 d (Test mat. analysis) (Initial concentration: 10 µg/L,	MCPA-thioethyl technical - Analytical purity: 97.3% [14C]-MCPA-thioethyl - Analytical purity: 99.4 % Klimisch 1 (reliable without restriction)	Simmonds R (2015) KCA 7.2.2.2/01

Method	Results	Remarks	Reference
	93.4% MCPA-thioethyl at time zero to 0% at day 0.5) after 0.5 d (Test mat. analysis) (Initial concentration: 100 µg/L, 92.7% MCPA-thioethyl at time zero to 6.3% at day 0.5) Transformation products: MCPA 4-chloro-2-methylphenol		
Test system: natural water / sediment (2 systems) Council Directive 91/414/EEC concerning the placing of plant protection products on the market. Part A 7.2.1. Rate and route of degradation in aquatic sytems. July 1991. Publication L230. Commission Directive 95/36/EC amending council directive 91/414/EEC concerning the placing of plant protection products on the market. Part 7.2.1.3.2. July 1995. Publication L172/8. SETAC. Aerobic aquatic degradation. In : Procedures of assessing the environmental fate and ecotoxicity of pesticides. Lynch M. (Ed). 1995	Half-life (DT_{50}): 0.07 d in freshwater at 20°C (Ostvaardersplassen) 0.08 d in entire system at 20°C (Ostvaardersplassen) 0.05 d in water at 20°C (Schoonrewoedsewiel) 0.06 d in entire system at 20°C (Schoonrewoedsewiel) Transformation products: MCPA 4-chloro-2-methylphenol	[ring-U-14C] Phenothiol - - Analytical purity: 99.0% (HPLC) 98.2% (radio-GC) 98.1% (TLC) Klimisch 1 (reliable without restriction)	Melkebeke et al (2002) KCA 7.2.2.3/01
Study type: adsorption/desorption (soil) batch equilibrium method OECD Guideline 106 (Adsorption - Desorption Using a Batch Equilibrium Method) JMAFF, 9 HohSan, No.: 5089, Test method for physical and chemical properties of pesticide: 10. Soil absorption Coefficient (1997)	Transformation products: no MCPA-thioethyl decomposed under the guideline test conditions. The report concluded that the absorption/desorption test is not critical for MCPA-thioethyl because of the rapid decomposition in soil media.	MCPA-thioethyl - Analytical purity: 100 % (HPLC) Klimisch 3 (not reliable)	Odanaka Y (1999) KCA 7.1.3.1.1/01
Study type: adsorption/desorption (soil) batch equilibrium method OECD Guideline 106 (Adsorption - Desorption Using a Batch Equilibrium Method)	Adsorption coefficient: Koc: 3736 at 20°C (% Org. C: 3.92) (Kenslow) Koc: 3981 at 20°C (% Org. C: 1.43) (Clipstone) Koc: 2872 at 20°C (% Org. C: 1.8) (Hareby) Koc: 3891 at 20°C (% Org. C: 0.66) (Lufa Speyer 2.3) Koc: 2855 at 20°C (% Org. C: 2.81) (South Witham)	MCPA-thioethyl technical - Analytical purity: 97.3% [14C]-MCPA-thioethyl - Analytical purity: 99.4 % Klimisch 1 (reliable without restriction)	Hawkins T and Simmonds M (2015) KCA 7.1.3.1.1/02

Method	Results	Remarks	Reference
	Koc: 3467 at 20°C (Mean value)		

5.1.1 Stability

Study 1: Slangen PJ. 2002 (KCA 7.2.1.1/01)

The hydrolytic degradation behaviour of ^{14}C-labelled MCPA-thioethyl in three buffer solutions was investigated.

The test solutions contained 0.93 µM MCPA-thioethyl (0.229 mg/L) and 0.02 M buffer (0.05% organic co-solvent). In an amber glass vessel, approximately 200 mL of test solution was incubated for 30 days at 20°C ± 2°C under aerobic and sterile conditions. Organic volatiles and CO_2 were trapped. Samples were taken at various time points during the study. Total activity in the samples and in the traps was determined by LSC. The distribution of activity in the samples and in the traps was determined by LSC; the distribution of activity in the samples between parent and metabolites was determined by TLC (3 methods).

At pH 9, the activity in the A+B traps never exceeded 0.2% of the initial test solution activity. Considerably more activity was trapped at pH 7 (4.8%) and pH 4 (8.9%) after 30 days of incubation. It was shown that this trapped activity in fact was not carbon dioxide but MCPA. No more that 0.02% of the initial activity was recovered in the organic volatile traps (pH 9 only). The activity in the test solution at pH 9 was between 97% and 103% of the activity recovered at t=0 but as a result of significant absorption of MCPA-thioethyl to the container walls, the activity in the test solutions at pH 4 and pH 7 decreased steadily to 68% by the end of the test.

^{14}C-labelled MCPA-thioethyl was hydrolysed at 20°C in buffer solutions of pH 4, 7 and 9. Rapid hydrolysis was observed at pH 9 (DT_{50} < 12 hours). The DT_{50} was 12.5 days at pH 7 and 23.5 days at pH 4. MCPA-thioethyl can therefore be considered moderately hydrolysing (pH 7, 20°C) according to the classification scheme.

At all pH values tested, MCPA was the major metabolite of the hydrolytic degradation of MCPA-thioethyl (maximum 31% at pH 4 after 30 days, 53% at pH 7 after 30 days and complete conversion at pH 9 within one week). The DT_{50} of MCPA could not be calculated because its amount in all test solutions increased or remained constant with time. MCPA appears hydrolytically stable at all three pH values tested.

Study 2: Wonders J, Slangen PJ & van Noorloos B. 2002 (KCA 7.2.1.1/02)

This report describes a study performed to investigate the hydrolytic behaviour of ^{14}C-labelled MCPA-thioethyl in two buffer solutions, pH 4 and pH 7. The test solutions contained 2.14 µM MCPA-thioethyl (0.527 mg/L) and 0.02 M buffer (0.62% organic co-solvent). Approximately 200 mL of test solution was incubated in amber glass vessels for up to 31 days at 20°C ± 2°C under anaerobic and sterile conditions. Organic volatiles and CO_2 were trapped.

Complete vessels were sampled after 0, 3, 6, 13, 20 and 31 days; an additional sampling point was included for pH 4 after 26 days. Total activity in the samples and in the traps was determined by liquid scintillation counting (LSC). The distribution of activity in the samples between parent and metabolites was determined by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC).

^{14}C-labelled MCPA-thioethyl was hydrolyzed at 20°C in buffer solutions of pH 4 and 7. The DT_{50} was 26.5 days at pH 4 and 7.4 days at pH 7; MCPA-thioethyl can therefore be classified as fairly hydrolysing (pH 7, 20°C).

At both pH 4 and pH 7, MCPA was the major metabolite of the hydrolytic degradation of MCPA-thioethyl. The DT_{50} of MCPA was estimated to be 43.4 days (pH 4) and 211 days (pH 7); MCPA can be classified as slightly hydrolysing.

These DT_{50} values were obtained by assuming, that any MCPA-thioethyl adsorbed to the container wall (and desorbed in the rinsate) could participate in the hydrolysis process and thus was considered in the calculations. In a second scenario, it may be assumed that all this adsorbed activity would have adsorbed to sediment or sludge particles under natural conditions, thereby not being available for hydrolysis. Based on this assumption, the DT_{50} values of MCPA-thioethyl and MCPA were recalculated based on the amounts in the test solution only. The DT_{50} of MCPA-thioethyl was 21 .8 days at pH 4 and 6.6 days at pH 7; the DT_{50} of MCPA was estimated to be 345 days (pH 4) and 159 days (pH 7).

Apart from MCPA, several (groups of) unknown metabolites were formed, depending on the pH of the test solution, which could be separated by TLC and/or HPLC. None of the unknown metabolites exceeded 10% of activity.

Study 3: Willems H. 2003 (KCA 7.2.1.2/01)

A 0.67 mg/L solution of MCPA-thioethyl in 0.02 M pH 4 buffered (phosphate), de-ionised, sterilised water was continuously irradiated for a period of 2.2 days under a sunlight simulating light source (Xenon lamp). The average temperature of the solution during irradiation was 23.8°C; a MCPA-thioethyl solution of identical composition was kept in the dark at approximately 25°C. Volatiles were trapped in a Tenax and soda lime trap.

The Xenon lamp intensity was such that the 2.2 day period of continuous irradiation under simulated sunlight conditions was equivalent to 3.0 days of natural sunlight at 40°N in summer (based on incident light intensity 300-400 nm). The test was terminated after 2.2 days because twice DT_{50} was reached.

During the test, radioactivity was lost due to un-trapped volatiles resulting in a mass balance of 81.2% after 2.2 days. These volatiles were characterised as unaltered MCPA-thioethyl and CO_2 in a preliminary test (mass balance 92.2% after 7 days).

MCPA-thioethyl degraded under the test conditions with a DT_{50} of 0.63 days in the irradiated solution; the DT_{50} of MCPA-thioethyl in the dark control was 4.38 days. The photolytic degradation rate constant was 0.94 d^{-1} (photolytic DT_{50}: 0.74 days under the test conditions and 1.01 days at 40°N in the summer). The quantum yield was 0.0107.

The first step in the photolytic degradation route is the transformation of MCPA-thioethyl to MCPA. MCPA is further transformed under the influence of light to a number of photodegradates, including 4-chloro-2-methyl phenol (CMP, or 2M4CP). MCPA and 2M4CP did not exceed 10% of applied radioactivity. One peak exceeded 10% of applied radioactivity; this was considered a polar compound based on its HPLC retention time, the presence of a shoulder may indicate the presence of another component.

Study 4: Haynes LM. 2015a (KCA 7.2.1.2/02)

The aqueous photolysis of [^{14}C]-MCPA-thioethyl in sterile phosphate buffer at pH 7 at a nominal concentration of 1 mg/L has been investigated. The study was conducted, under sterile conditions, at

25 ± 3°C, with continuous irradiation under artificial sunlight for 40 hours (which equated to 3.29 days natural summer sunlight at latitude 40°N). The artificial sunlight was provided by a xenon arc lamp with filters to cut off any radiation below 290 nm. These conditions were maintained throughout the study.

A preliminary study was conducted to determine the definitive study irradiation times. In the definitive study, duplicate (irradiated) and single (non-irradiated) vessels were sampled at time zero and after 2, 4, 8, 16, 24, and 40 hours of continuous irradiation. The quantum yield was determined, using a pyridine/4-nitroacetophenone actinometer, to measure the irradiation in separate test vessels.

Initial concentrations of the treatment solutions were 1.01 – 1.12 mg/L, with <1% acetonitrile present as a co-solvent. The radiochemical purity of the test item was determined to be > 97% by both reverse phase HPLC and normal phase TLC.

Mean recoveries of applied radioactivity (% AR) were between 90.2 – 96.3% AR (mean of 93.6% AR) for irradiated buffered water and 91.6 – 100.5% AR (mean of 96.8% AR) for the non-irradiated samples. Volatile radioactivity was not collected during the definitive study.

Mean concentrations of radioactivity for the combined water and solvent rinse were in the range 0.952 – 1.01 mg/L (mean of 0.980 mg/L) for the irradiated samples and 0.925 – 1.03 mg/L (mean of 0.989 mg/L) for the non-irradiated samples.

Portions of each sample were taken for chromatographic analysis by reverse phase high performance liquid chromatography (HPLC) using ^{14}C-flow-through detection techniques. Under irradiated conditions, MCPA-thioethyl declined from 93.0% AR (at time zero) to 26.1% AR after 40 hours. Five photodegradates accounted for >5% AR of which 2 were identified. D21 accounted for a mean maximum of 5.4% AR at 8 hours before declining to 2.7% AR after 40 hours of continuous irradiation; D21 was identified by reverse phase HPLC, normal phase TLC chromatography and LC-MS/MS as MCPA. D17 accounted for a mean maximum of 8.2% AR after 40 hours of continuous irradiation and was identified by LC-MS/MS as (4-chloro-2-methylphenoxy)methyl formate.

D19 accounted for a maximum of 6.6% AR after 16 hours of continuous irradiation before declining to 3.0% AR at 40 hours, D24 accounted for a mean maximum of 5.4% AR after 40 hours of continuous irradiation; both remained unidentified by LC-MS/MS due to poor ionisation. Photodegradate D2 accounted for a mean maximum of 5.2% AR after 40 hours of continuous irradiation; investigations supporting the theory that this degradate was associated with dissolved $^{14}CO_2$.

The DT_{50} and DT_{90} values of MCPA-thioethyl in sterile phosphate buffer at pH 7 under continuous Suntest irradiation were calculated to be 20.6 hrs and 68.6 hours respectively. The DT_{50} and DT_{90} values calculated with respect to days of equivalent summer sunlight at 40°N were 1.69 and 5.63 days respectively. The DT_{50} and DT_{90} values of MCPA-thioethyl in non-irradiated sterile pH 7 buffer were calculated to be 592 hours and >1000 hours respectively.

The DT_{50} and DT_{90} values of MCPA, in sterile buffer at pH 7 under continuous Suntest irradiation, were calculated to be 3.33 and 11.1 hours respectively. The DT_{50} and DT_{90}, calculated with respect to days of equivalent summer sunlight at 40ºN, were 0.273 and 0.911 days respectively. The DT_{50} and DT_{90} values of MCPA, in non-irradiated sterile phosphate buffer at pH 7, were both calculated to be >1000 hours.

The quantum yield of MCPA-thioethyl in irradiated sterile phosphate buffer at pH 7 was determined to be 0.00337.

Study 5: Haynes LM. 2015b (KCA 7.2.1.3/01)

The aqueous photolysis of [^{14}C]-MCPA-thioethyl in sterile natural water at a nominal concentration of 1 mg/L has been investigated. The study was conducted, under sterile conditions, at 25 ± 3°C, with continuous irradiation under artificial sunlight for 40 hours (which equated to 3.55 days of natural summer sunlight at latitude 40°N). The artificial sunlight was provided by a xenon arc lamp with filters to cut off any radiation below 290 nm. These conditions were maintained throughout the study. Non-irradiated samples were maintained in an incubator at 25 ± 3°C.

A preliminary study was conducted to determine the irradiation times for the definitive study. In the definitive study, duplicate (irradiated) and single vessels (non-irradiated) were sampled at time zero and after 2, 6, 14, 24, 36, and 40 hours of continuous irradiation.

Initial concentrations of the treatment solutions were 0.985 - 1.06 mg/L, with <1% acetonitrile present as a co-solvent. The radiochemical purity of the test item was determined to be > 97% by both reverse phase HPLC and normal phase TLC.

Mean recoveries of applied radioactivity (% AR) were between 92.6 - 101.9% AR (mean of 96.4% AR) for irradiated samples and 95.5 - 102.5% AR (mean of 98.6% AR) for the non-irradiated samples. Volatile radioactivity was not collected during the definitive study. Mean concentrations of radioactivity for the combined water and solvent rinse were in the range 0.944 - 1.04 mg/L (mean of 0.975 mg/L) for the irradiated samples and 0.952 - 1.05 mg/L (mean of 0.988 mg/L) for the non-irradiated samples.

Portions of each sample were taken for chromatographic analysis by reverse phase high performance liquid chromatography (HPLC) using ^{14}C-flow-through detection techniques. Under irradiated conditions, MCPA-thioethyl declined from 96.0% AR at time zero to 15.8% AR after 40 hours. Four photodegradates accounted for >5% AR of which 2 were identified: D32 accounted for a mean maximum of 16.7% AR at 24 hours before declining to 3.9% AR after 40 hours; D32 was identified by reverse phase HPLC, normal phase TLC chromatography and by LC-MS/MS as MCPA. D28 accounted for a mean maximum of 6.6% AR after 36 hours of continuous irradiation and was identified by LC-MS/MS as (4-chloro-2-methylphenoxy)methyl formate. D30, mean maximum of 3.2% AR at 24 hours was tentatively identified as 4-chloro-2-methylphenol (2M4CP).

Additionally two photodegradates remained unidentified: D34 accounted for a mean maximum of 6.9% AR after 36 hours of continuous irradiation before declining to 3.1% AR at 40 hours; D34 could not be identified by LC-MS/MS due to poor ionisation. D10 accounted for mean maximum of 9.7% AR after 36 hours of irradiation. This degradate remained unidentified however, following additional investigations, the proportion of radioactivity associated with photodegradate D10 was shown to decrease after acidification suggesting that degradate D10 may be associated with volatile radioactivity (such as dissolved ^{14}CO2).

Under non-irradiated conditions, MCPA-thioethyl declined from 96.9% AR at 2 hours to 64.2% AR at 40 hours. The main degradation product, D32, was identified as MCPA and this accounted for a maximum of 30.5% AR at 40 hours. One other degradate, D30, was tentatively identified as 4-chloro-2-methylphenol (2M4CP), based on its HPLC retention time and accounted for a maximum of 1.2% AR at 2 hours declining to 0.8% AR after 40 hours.

The DT_{50} and DT_{90} values of MCPA-thioethyl, in irradiated sterile natural water under continuous Suntest irradiation, were calculated to be 18.1 and 60.1 hours respectively. The DT_{50} and DT_{90}, values calculated with respect to days of equivalent summer sunlight at 40ºN, were 1.61 and 5.33 days respectively. The DT_{50} and DT_{90} values of MCPA-thioethyl, in non-irradiated sterile natural water, were calculated to be 72.0 and 239 hours respectively.

The DT_{50} and DT_{90} values of MCPA, in irradiated sterile natural water under continuous Suntest irradiation, were calculated to be 6.5 and 21.6 hours respectively. The DT_{50} and DT_{90}, calculated with respect to days of equivalent summer sunlight at 40ºN, were 0.58 and 1.92 days respectively. The DT_{50} and DT_{90} values of MCPA, in non-irradiated sterile natural water, were calculated to be 256 and 850 hours respectively.

5.1.2 Biodegradation

Study 1: Brunswik-Titze A. 2015 (KCA 7.2.2.1/01)

Three reactors containing the test item, three reactors containing only inoculum (blank), three reactors containing the reference compound and one reactor containing test item and reference compound (toxicity control) were set up. The inoculum was activated sludge diluted with mineral medium to give a concentration of 30 mg/L dry solids. Approximately 56.0 mg of the test item were added to the three test vessels (corresponding to a TOC concentration of 20.0 mg/L). The reference compound was added to the reference vessels; test item and reference compound were added to the toxicity control vessel. The flasks were aerated with CO_2 free air.

The CO_2 produced in the reactors was absorbed in two gas wash bottles in series each containing 0.2 M NaOH. On days 4, 7, 11, 14, 21 and 28, the first of the two CO_2-absorber flasks connected in line was sampled and the inorganic carbon (IC) contents were determined. On day 28, hydrochloric acid was added to each reactor to release the CO_2 dissolved in water. On day 29 the IC was determined in both CO_2-absorber flasks. IC measurements were performed with a total carbon analyser using a non dispersive infrared detector.

The reference compound, sodium benzoate reached the pass levels for ready biodegradability (60%) within 4 days.

The degradation extent in the toxicity control was higher than 25% within 14 days (43.3% on day 14). Therefore the test item had no inhibitory effect on the inoculum.

The mean CO_2-evolution of the blank flasks was 34.8 mg/L after 28 days after acidification. Before adding the test item, the IC in the reactor was determined, but only insignificant amounts of IC (0.7 mg/L) were found. The IC-concentrations of the NaOH in the second CO_2-absorber flasks, used as protective flasks, were below 10 ppm. The temperature was 22.2 – 22.9°C throughout the whole study and the aeration rate was in the acceptable range.

The variation in the extent of degradation of MCPA-thioethyl was high; this was considered likely to be due to the insolubility of the test item which resulted in formation of clumps of test item leading to differences in bioavailability in the different test reactors.

The criteria for a valid test were met; the extent of biodegradation of MCPA-thioethyl was 53.6% after 28 days incubation. Since the pass level for ready biodegradability is ‘60% within 28 days’, this study indicates that MCPA-thioethyl does not meet the criteria to be considered as ‘Readily biodegradable’.

5.1.2.1 Biodegradation estimation

Estimation not required as studies provided.

5.1.2.2 Screening tests

No additional data.

5.1.2.3 Simulation tests

Study 1: Simmonds R. 2015 (KCA 7.2.2.2/01)

The time course and concentration dependency of the degradation of [14C]-MCPA-thioethyl was investigated under aerobic conditions in a "pelagic" test system (natural fresh water) at 20 ± 2°C, in the dark, for a period of 30 days. This study was carried out using water from Carsington water, a reservoir storing water from the river Derwent and also smaller quantities of water draining off grassland surrounding the reservoir.

Flasks containing the test water were each treated with 1 mL of the corresponding solution of the [14C]-test item treatment, adding the solution drop-wise onto the water surface. The test was performed at two test concentrations, the average application rates of MCPA-thioethyl achieved were 10.0 µg/L and 101.9 µg/L. Sterile, positive and solvent controls were included.

For each of the two dose rates duplicate flasks and their associated traps were removed at each sampling time point (0, 0.02, 0.04, 0.08, 0.5, 1, 3, 7, 14, 21 and 30 days). Dissolved $14CO_2$ and the total activity in the samples were determined. Water samples were analysed by high performance liquid chromatography (HPLC) with selected samples also being analysed by thin layer chromatography (TLC) to confirm the identity of the parent and metabolites.

The recovery for the positive control samples on day 14, averaged 94.1% of the applied activity, of which 77.0% was recovered as $14CO_2$ (i.e. [14C]-benzoic acid mineralised). This demonstrated the efficiency of the work-up method in quantifying $14CO_2$ formed; precipitation of potassium hydroxide trap samples with barium chloride and sodium carbonate confirmed that $14CO_2$ was the only form of activity in the traps.

For both dose rates the overall material balances were good with mean values of 97.2 and 95.2% AR for the 10 µg/L and 100 µg/L dose rates respectively. Individual recoveries were all within the range of 90–110%.

Total levels of test item mineralisation were very low for both dose rates reaching a maximum of 3.5% AR by day 21 at the 10 µg/L dose level.

In the 10 µg/L test MCPA-thioethyl declined from 93.4% at time zero to 0% at Day 0.5; this decline corresponded to an increase in MCPA from 0% at time zero to 97.5% at Day 0.5. Levels of MCPA then remained reasonably constant for the remainder of the study ranging from 84.2 – 96.9% AR. Low levels of 4-chloro-2-methylphenol were detected throughout the study reaching a maximum of 2.1% AR at Day 0.04. Numerous minor unknowns were observed throughout the course of the study none of which accounted for >3.0% AR at any one time point.

In the 100 µg/L test MCPA-thioethyl declined from 92.7% at time zero to 6.3% at Day 0.5; this decline corresponded to an increase in MCPA from 1.0% at time zero to 89.3% at Day 0.5. Levels of MCPA continued to increase to a maximum of 96.2% at Day 3 then slowly declined to 91.8% at the end of the study. Low levels of 4-chloro-2-methylphenol were detected throughout the study reaching a maximum of 1.6% AR at Day 0.5. Numerous minor unknowns were observed throughout the course of the study none of which accounted for >0.5% AR at any one time point.

In the sterile control systems MCPA-thioethyl declined from 23.2 and 29.7% AR at Day 1 (10 and 100 µg/L treatment levels respectively) to 0% AR at Day 30. Levels of MCPA increased from 70.0

and 64.2% at Day 1 to 92.0 and 95.7% AR at Day 30. This confirmed that the degradation of MCPA-thioethyl was mostly abiotic.

[14C]-MCPA-thioethyl was shown to degrade rapidly to MCPA in the test system, consisting of natural water incubated in the dark at 20 ± 2°C, however mineralisation to CO_2 remained low over the 30 day duration of the study. Degradation of MCPA-thioethyl was also observed in sterile control flasks, albeit at a slower rate, indicating degradation was not entirely biotic in nature. Rapid mineralisation in the positive control flasks demonstrated that the test water had acceptable levels of biological activity for the test.

Study 2: Melkebeke, T., van Noorloos B. & Wonders J. 2002 (KCA 7.2.2.3/01)

MCPA-thioethyl (Phenothiol) was incubated aerobically in the laboratory in two non-contaminated water/sediment systems from Oostvaardersplassen (OVP) and Schoonrewoerdsewiel (SW) at 20 ± 2°C in the dark for 97 days. The test substance concentration in the water layer was approximately 55 µg/L and 111 kBq per vessel. The concentration corresponds to a field application rate of 160 g ai/ha (equivalent to about 4.5 times GAP in citrus), directly sprayed on surface water and homogeneously distributed in a ditch with a 30 cm water layer.

MCPA-thioethyl dissipated quickly from the water layer in both water/sediment systems: the DT_{50} values for dissipation of MCPA-thioethyl from the Oostvaardersplassen and Schoonrewoerdsewiel water layers were 0.07 and 0.05 days, respectively. DT_{50} values were 0.24 (OVP) and 0.15 days (SW). DT_{50} values for the major metabolite, MCPA in the water layer were 19 days (OVP) and 17 days (SW).

Dissipation of MCPA-thioethyl from the water layer was mainly the result of degradation to MCPA, followed by transfer of MCPA to the sediment and mineralisation. The sum of unknowns never exceeded 5.3% of applied in the water layers. No relevant (>10%) metabolites were therefore observed in the water layers.

MCPA-thioethyl never dissipated towards the sediment (maximum value 0.7% after 5 hours), but its degradation product MCPA did. Dissipation of MCPA from the sediment was the result of mineralisation, formation of bound residues and the formation of metabolites. The amount of bound residues increased gradually to 30% (OVP) and 31% (SW) after 97 days of incubation. HPLC analysis showed one relevant metabolite in the SW sediment at t=14, 21 and 23 days (maximum value 13.1%; t=21). This metabolite was identified as 4-chloro-2-methylphenol; TLC results confirmed the presence of this metabolite.

In both systems as a whole (water + sediment), the DT_{50} of MCPA-thioethyl was approximately equal to that of the water layer (0.08 days for OVP and 0.06 days for SW). The DT_{50} was 0.26 days (OVP) and 0.18 days (SW). The DT_{50} and DT_{90} of MCPA in the total system were 25 and 82 days (OVP) and 19 and 62 days (SW).

Mineralisation was a major degradation process in the water/sediment systems (OVP: maximum 61% after 97 days, SW: maximum 68% after 63 days).

According to the classification scheme, MCPA-thioethyl can be considered readily degradable in the two water/sediment systems tested; MCPA can be considered fairly degradable in the OVP system and readily degradable in the SW system.

5.1.3 Summary and discussion of degradation

In a ready biodegradation study, MCPA-thioethyl was found not to be ready biodegradable.

In the aquatic environment, MCPA-thioethyl dissipates very quickly from the water layer (DT_{90} <1 day), degrading to MCPA by biotic and abiotic routes, followed by transfer of MCPA to sediment and mineralisation. One further metabolite: 2M4CP was identified as 'significant', but levels in the whole water sediment system declined after 21 days.

MCPA-thioethyl degrades rapidly by photolysis with a DT_{50} equivalent to summer sunlight at 40°N of 1.69 days; to a number of minor (<10% AR) degradates, In hydrolysis studies, it is classified as 'fairly hydrolysing' with DT50s of 26.5 days and 7.4 days at pH 4 and 7 respectively.

Conclusions:
Simulation tests show rapid primary biodegradation of MCPA-thioethyl in the environment. According to the Guidance on the Application of CLP criteria (Version 4.1 – June 2015) data on primary degradation can only be used to show rapid degradation of substance where it is demonstrated that the degradation products shall not be classified as hazardous to the environment, i.e. that they do not fulfil the classification criteria. Main metabolite identified during degradation of MCPA-thioethyl is MCPA. MCPA is included in Annex VI of CLP Regulation. In Annex VI to CLP Regulation MCPA is classified as hazardous to the environment – Aquatic Acute 1, H400; Aquatic Chronic 1, H410.
Due to the fact that one of the metabolites of MCPA-thioethyl is classified as hazardous to the environment, data on primary degradation can not be used to demonstrate that MCPA-thioethyl is rapidly degradable.

Taking into account all available data it can be concluded that MCPA-thioethyl is not readily degradable.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Study 1: Odanaka Y. 1999 (KCA 7.1.3.1.1/01)

The purpose of this study was to examine the sorption properties of MCPA-thioethyl to soil in the environment. Four Japanese standard soils were used for the screening test (adsorption/desorption test) and additional examination (mass balance).

MCPA-thioethyl was found unsuitable for the adsorption/desorption test due to its instability. The mass balance of MCPA-thioethyl was less than the recommended criterion of the Guideline (70%). The conclusion of the study was that the soil media is not important for MCPA-thioethyl; MCPA-thioethyl rapidly decomposed in soil media under the test conditions.

Study 2: Hawkins T & Simmonds M. 2015 (KCA 7.1.3.1.1/02)

The adsorption/desorption characteristics of MCPA-thioethyl were studied in five EU soils using the batch equilibrium method. The soils used were Kenslow loam (UK, pH 5.0, 3.92% organic carbon), Clipstone loamy sand (UK, pH 5.2, 1.43% organic carbon), Hareby clay (UK, pH 7.6, 1.80% organic carbon), Lufa Speyer 2.3 sandy loam (Germany, pH 6.2, 0.66% organic carbon), and South Witham sandy clay loam (UK, pH 7.6, 2.81% organic carbon).

The adsorption phase of the study was carried out using pre-equilibrated soils with [^{14}C]-MCPA-thioethyl at concentrations of approximately 0.4, 0.3, 0.2, 0.1 and 0.004 mg L^{-1} in the dark and at 20 ± 2°C for 30 minutes for all soils. A soil solution ratio of 1:80 for all soils was used. The desorption phase of the study was not carried out due to the limited stability of [^{14}C]-MCPA-

thioethyl under the test conditions, instead, extraction of the soil was conducted directly after the removal of adsorption supernatant.

The aqueous supernatant (after adsorption) and solvent extract were separated by centrifugation and analysed by liquid scintillation counting (LSC) and by HPLC (top three concentrations in the definitive stage). After extraction, the soil was combusted and the trapped CO_2 analysed by LSC. The adsorption parameters were calculated using the direct method, where concentrations of [^{14}C]-MCPA-thioethyl are based on recovered test item, then plotted using the Freundlich isotherm.

Soils were sterilised using the gamma irradiation technique. For the definitive stage of the study the soils were also autoclaved prior to measuring soils into tubes.

The Tier 1 experiments conducted with all soils found that [^{14}C]-MCPA-thioethyl rapidly degraded under the test conditions. In order to progress to the later stages of the study a "stability window" adsorption time of 30 minutes was established, after which time sufficient parent material remained to determine the distribution of [^{14}C]-MCPA-thioethyl between soil and solution. Due to the limited stability of [^{14}C]-MCPA-thioethyl, a desorption phase was not attempted, and the soils were immediately extracted, following adsorption, using a single addition of chosen solvent to minimise the time between the dosing of the test systems and the analysis of both phases. LSC and HPLC analysis of the adsorption supernatants and extract solutions was performed. The parental mass balance in the five soils ranged from 75.8% to 92.8%. Due to the short equilibration time an equilibrium between soil and solution was not reached, and thus the determined K_{oc} will represent a lower limit.

The overall material balances in the definitive study were determined by LSC of the supernatants after adsorption, solvent extraction and combustion of the remaining soils. The overall material balance for individual samples was in the range of 87.3 to 95.0% for the Kenslow loam (mean 91.6%), 86.6 to 92.6% for the Clipstone loamy sand (mean 90.1%), 86.1 to 93.5% for the Hareby clay (mean 91.0%), 87.5 to 93.6% for the Lufa Speyer 2.3 sandy loam (mean 90.4%) and 90.5 to 97.6% for the South Witham sandy clay loam (mean 94.9%).

In the definitive adsorption test, the amount of applied test material adsorbed ranged from 57.3 to 61.8% in the Kenslow loam, 35.0 to 39.8% in the Clipstone loamy sand, 36.6 to 45.4% in the Hareby clay, 21.2 to 26.6% in the Lufa Speyer 2.3 sandy loam and 44.7 to 53.6% in the South Witham sandy clay loam.

The calculated adsorption constants K_f of the Freundlich isotherms for the five test soils ranged from 25.7 to 146.5. The Freundlich exponents 1/n displayed a degree of non-linearity (values ranging from 0.928 to 0.972), thus indicating an increased degree of adsorption at lower concentrations. The adsorption K_{oc} values ranged from 2855 to 3981.

There was significant correlation between adsorption and organic carbon content for the investigated soils, with a plot of K_f versus organic carbon giving a correlation of 0.93.

The mean determined K_{OC} was 3467 mL g^{-1} with a mean 1/n value of 0.949. Consequently, MCPA-thioethyl would be classified as being immobile in soil according to the Briggs classification and slightly mobile according to the McCall classification. The determined K_{oc}, however, represents a lower limit due to the necessary restriction on the adsorption period used in the study, and the direct method by which the soil and solution concentrations are calculated.

5.2.2 Volatilisation

The vapour pressure of pure MCPA-thioethyl is 1.30×10^{-2} Pa at 25°C.

Henry's Law Constant is 2.102×10^{-1} Pa m^3/mol at 25°C.

Both figures are in the List of Endpoints (SANCO/4062/2001 – final 11 July 2008).

5.2.3 Distribution modelling

Not applicable

5.3 Aquatic Bioaccumulation

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

Although the MCPA-thioethyl log Pow is > 4 being 4.35 at pH 7 and 20°C (Hitchens & Frake (2014); KCA 2.7/01), bioaccumulation is highly unlikely to occur since predicting from mammalian metabolism, MCPA-thioethyl would be very rapidly metabolised to MCPA in fish and aquatic organisms. Taking into account the partition coefficient Pow (log Pow << 3) for MCPA, and the solubility in water (26.2 mg/L at pH 5 and 25°C and 293.9 mg/L at pH 7 and at 25°C) (MCPA Review Report, SANCO/4062/2001-final, 11 July 2008), no significant bioaccumulation can be expected in fish.

Comparison of the NOEC from the MCPA acute 96 h studies with the 28 day study indicates very similar values. Had there been any accumulation of MCPA in fish, these values would have been significantly different.

Further, using EPISuite, the predicted (QSAR) BCF was 344.5L/Kg (acceptable) using MCPA-thioethyl Kow of 4.35.

5.3.1.2 Measured bioaccumulation data

No further information required.

5.3.1.3 Summary and discussion of aquatic bioaccumulation

Although the MCPA-thioethyl log Pow is > 4, taking into consideration the very rapid metabolism to MCPA after intake, exposure leading to MCPA-TE bioconcentration is deemed not likely to occur (please also refer to 5.3.1.1 above).

5.4 Aquatic toxicity

Table 22: Summary of relevant information on aquatic toxicity

Method	Results	Remarks	Reference
Rainbow Trout (*Oncorhynchus mykiss*) Freshwater, semi-static Nominal concentrations: 0.028, 0.040, 0.069, 0.117 and 0.198 mg/L Mean measured concentrations: 0.015, 0.026, 0.037, 0.059 and 0.104 mg /L. OECD Guideline 203 (Fish, Acute Toxicity Test)	LC_{50} (96 h): 0.046 mg/L (mean measured) based on: mortality NOEC (96 h): 0.026 mg/L (mean measured) based on lack of sub-lethal effects.	MCPA-thioethyl Test material purity: 99.0% Klimisch 1 (reliable without restriction)	Juckeland D* (2014) KCA 8.2.1/01 * Key studies for consideration of MCPA-thioethyl classification
Rainbow Trout (*Oncorhynchus mykiss*) Fresh water, semi-static Test material purity: (Purity: IUCLID technical dossier) Nominal concentrations: 0.05, 0.10, 0.20, 0.40 & 0.80 mg/L OECD Guideline 204 (Fish, Prolonged Toxicity Test)	LOEC (21 d): 0.4 mg/L(nominal) based on: mortality NOEC (21 d): 0.2 mg/L(nominal) based on lack of sub-lethal effects	MCPA-thioethyl Purity: 93.4% Klimisch 1 (reliable without restriction)	Grunert B (1991a) KCA 8.2.2/01
Daphnia magna Freshwater, semi-static Nominal concentrations: 0.100, 0.150, 0.225, 0.338 and 0.507 mg/L Mean measured concentrations: 0.069, 0.105, 0.155, 0.300 and 0.375 mg/L. OECD Guideline 202 (*Daphnia* sp. Acute Immobilisation Test)	EC_{50} (48 h): 0.131 mg/L test mat. (meas. (geom. mean)) based on: mobility NOEC (48 h) : 0.105 mg/L (meas. (geom. mean)) based on: mobility	MCPA-thioethyl Test material purity: 99.0% Klimisch 1 (reliable without restriction)	Mantilacci S (2014a) KCA 8.2.4/01
Daphnia magna Fresh water, semi-static Nominal concentrations: 0.009, 0.036, 0.144, 0.575 and 2.3 mg/L OECD Guideline 202 (Daphnia sp., Acute Immobilisation Test and Reproduction Test, part II, adopted April 4, 1984)	EC_{50} (21 d):0.06 mg/L(nominal) based on mortality NOEC (21 d): 0.009 mg/L(nominal) based on : mortality, reproduction rate, length of time for appearance of the first brood & other observed effects LOEC (21 d): 0.036 mg/L	MCPA-thioethyl Test material purity: 93.4% Klimisch 1 (reliable without restriction)	Grunert B* (1991b) KCA 8.2.5.1/01 * Key studies for consideration of MCPA-thioethyl classification
Scenedesmus subspicatus (now *Desmodesmus subspicatus*) (algae) Freshwater, static Nominal concentrations: 0.009, 0.018, 0.036, 0.072, 0.144 , 0.288 0.575, 1.15 and 2.3 mg/L. OECD Guideline 201 (Alga, Growth Inhibition Test)	NOEC (72 h): 0.009 mg/L (nominal) based on: growth rate E_rC_{50} (72 h): > 2.3 mg/L(nominal) based on: growth rate	MCPA-thioethyl Test material purity: 93.4% Klimisch 1 (reliable without restriction)	Grunert B (1991c) KCA 8.2.6/02

Selenastrum capricornutum (now: *Pseudokirchnerella subcapitata*) (algae) Freshwater, static Nominal test concentration: 1.0, 2.2, 4.6, 10.0 and 22 mg/L equivalent to 0.2, 0.44, 0.92, 2.0 and 4.4 mg/L EEC Methods for Determination of Ecotoxicity Annex to Directive 92/69/EEC (O.J. No. L383A, 29.12.92) Part C, Method 3 equivalent or similar to OECD Guideline 201 (Alga, Growth Inhibition Test)	EC_{50} (72 h): 0.92 mg/L act. ingr. (nominal) based on: area under growth rate curve EC_{50} (72 h): 1.38 act. ingr. (nominal) based on: growth rate NOEC (72 h): 0.44 mg/L act. ingr. (nominal) based on: growth rate	Test material: 20% EC formulation of Phenothiol Klimisch 1 (reliable without restriction)	Bell G (1995) KCA 8.2.6/01
Lemna minor (aquatic plants) Freshwater, semi-static Nominal concentrations: 0.022, 0.070, 0.223, 0.713 and 2.280 mg/L Mean measured concentrations: 0.020, 0.051, 0.173, 0.535 and 1.593 mg/L OECD Guideline 221 (Lemna sp. Growth Inhibition test)	EyC_{50} (7 d): 1.435 mg/L test mat. (meas. (geom. mean)) based on: growth rate based on the fronds number NOErC and NOEyC (7 d): 0.051 mg/L test mat. (meas. (geom. mean)) based on: growth rate based on the fronds number EyC50 (7 d): 1.935 mg/L test mat. (meas. (geom. mean)) based on: growth rate based on the dry weight NOEyC (7 d): 0.051 mg/L test mat. (meas. (geom. mean)) based on: growth rate based on the dry weight	MCPA-thioethyl Test material purity: 99.0% Kilmisch 1 (reliable without restriction)	Mantilacci S (2014b) KCA 8.2.7/01

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

One valid GLP acute toxicity study is available.

Study 1: Juckeland D, 2014 (KCA 8.2.1/01)

The purpose of the study was to determine the acute toxicity of the test item to rainbow trout, characterised by the median lethal concentration 96 hours after application (96-hour LC_{50}).

The test was performed under semi-static conditions using rainbow trout *(Oncorhynchus mykiss*) as a representative test organism for aquatic vertebrates according to the OECD Guideline 203.

A semi-static dose response test was conducted at 0.024, 0.040, 0.069, 0.118 and 0.198 mg test item/L with an untreated group (with solvent). The corresponding geometrical mean measured a.i. concentrations at 96 hours were 0.015, 0.026, 0.037, 0.059 and 0.104 mg test item/L. For each concentration 1 replicates of 10 fish were prepared and placed into stainless steel containers of 10 L volume.

The test organisms were exposed to the test solutions for 96 hours.

The mortality was recorded at 3, 6, 24, 48, 72 and 96 hours. Fish were considered dead if there was no visible movement (e.g. gill movements) and if touching of the caudal peduncle produced no reaction. Dead fish were removed when observed.

The 96 hour LC_{50} of MCPA-thioethyl was calculated to be 0.046 mg test item/L based on geometric mean measured concentrations (0-96 hours). The 96 hour NOEC (no observed effect concentration) was determined to be 0.026 mg test item/L and the LOEC, 0.037 mg test item/L.

5.4.1.2 Long-term toxicity to fish

One valid GLP study assessing the long-term toxicity to MCPA-thioethyl to fish is available.

Study 1: Grunert B 1991a (KCA 8.2.2/01)

The effect of Phenothiol (MCPA-thioethyl) (purity 93.4%) on long-term toxicity to rainbow trout was assessed in a semi-static test over 21 days as per GLP regulations and according to OECD guideline 204.

Groups of 10 Rainbow trout (*Salmo gairdneri*) were exposed to 0, 0.05. 0.10, 0.20, 0.40 and 0.80 mg Phenothiol/L with renewal of the test solution after 48/72 hrs.

The mortality and abnormal signs were observed daily. The median weight and length of each dose level group were recorded at the end of the test and compared with the median values of one representative group at the start of the experiment. The LOEC, LOAEC and NOEC values were calculated.

The fish of control and lowest test concentration showed neither mortality nor any visible sign of abnormality during the test time of 21 days. In the test concentration of 0.1 mg/L of Phenothiol (MCPA-thioethyl) a dead fish was recognised after 2 days, whereas the fishes of 0.2 mg/L concentration showed neither mortality nor abnormalities during the test. This death was deemed not treatment–related.

Death and abnormal responses of fishes at two highest concentrations were observed. The lowest tested concentration of Phenothiol (MCPA-thioethyl) at which the test substance had lethal effect (LOEC) was 0.4 mg/L. The lowest tested concentration of Phenothiol (MCPA-thioethyl) at which the test substance was observed to have an effect other than lethal one (LOAEC) was 0.4 mg/L.

The highest tested concentration of Phenothiol (MCPA-thioethyl) at which no statistically significant lethal or other effect was observed (NOEC) is 0.2 mg/L.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

One valid GLP study assessing the short-term toxicity to MCPA-thioethyl to aquatic invertebrate is available.

Study 1: Mantilacci S, 2014a (KCA 8.2.4/01)

The purpose of the study is to assess the effects of test item MCPA-thioethyl on *Daphnia magna* after 48 hours of exposure, in a semi-static acute test according to GLP principles.

A semi-static dose response test was conducted at 0.100, 0.150, 0.225, 0.338 and 0.507 mg/L of MCPA-thioethyl for 48 hours, with two untreated group (without and with solvent). For each concentration 4 replicates of 5 daphnids were prepared, placed into glass vessels containing each 50 mL of solution.

The test organisms were exposed to the test solutions for 48 hours. The number of mobile and immobile daphnids was counted at 24 and 48 hours after the start of the test.

In order to check the testing procedure and the quality of *Daphnia magna* breeding, an immobilisation test is performed twice a year, using potassium dichromate as toxic reference substance.

The evaluation of endpoints was based on the geometric means of measured concentrations of MCPA-thioethyl. For the treated groups these were 0.069, 0.105, 0.155, 0.300 and 0.375 mg/L.

The 48 hour EC_{50} was 0.131 mg/L and the NOEC, 0.105 mg/L.

5.4.2.2 Long-term toxicity to aquatic invertebrates

One valid GLP study assessing the long-term toxicity to aquatic invertebrates is available.

Study: Grunert B, 1991b (KCA 8.2.5.1/01)

The effect of Phenothiol (MCPA-thioethyl) (purity 93.4%) on the reproduction and survival rate of *Daphnia magna* was investigated in a semi-static test over 21 days according to OECD guideline 202.

Forty *Daphnia magna* (divided into 8 groups of five animals) per concentration were exposed to MCPA-thioethyl technical for 21 days in a semi-static test condition with renewal of test solution three times/week. The following concentrations are used: 0.009, 0.036, 0.144, 0.575, 2.3 mg/L of MCPA-thioethyl. Mortality of parental animals was recorded daily until to 96 hours and thereafter three times/week. The new-born young of F1 generation were counted three times a week and after examination were poured away. The EC_{50} value was calculated using the Litchfield and Wilcoxon standard procedures.

Daphnia mortality at 48 hours (LC_{50}) was calculated as the geometric mean of 2.3 mg/L (100% mortality) and 0.144 mg/L (0% mortality) and resulted 0.58 mg/L. (2.3 mg/L represents the maximum solubility of MCPA-thioethyl in water). Only the test concentration of 0.009 mg/L MCPA-thioethyl showed no statistical difference of mortality rate versus the control at 21 days (LOEC value). The 21 days EC_{50} value was 0.06 mg/L. The highest concentration which did not affect the reproduction rate at 21 days (NOAEC value) was 0.144 mg/L. The lowest tested concentration at which significant difference was found versus the control (LOAEC value) was 0.036 mg/L.

The highest tested concentration at which no significant difference is found versus the control with respect to mortality, reproduction rate, length of time for appearance of the first brood and other observed effect (NOEC value) is 0.009 mg/L MCPA-thioethyl.

5.4.3 Algae and aquatic plants

Two studies assessing the toxicity of Phenothiol (MCPA-thioethyl) to various algae species and aquatic plants are available.

Study 1: Bell, G; 1995 (KCA 8.2.6/01)

The effects of Phenothiol (as a 20% EC formulation) on algal growth of the aquatic plant *Selenastrum capricornutum,* Strain No.CCAP 278/4 after 72 h exposure was assessed in a static growth inhibition test as per GLP regulations and according to OECD guideline 201.Methods:

Algal cultures were exposed to five test concentrations of Phenothiol 20% EC plus one untreated control. Concentrations of the formulation were 1.0, 2.2, 4.6, 10 and 22 mg/L. Equivalent concentrations of the a.i. were 0.2, 0.44, 0.92, 2.0 and 4.4 mg/mL. Cultures were incubated on an orbital shaker under continuous illumination at 23°C. Growth was monitored daily by direct cell counts of each culture.

All test and control cultures were inspected microscopically at 72 hours. There were no abnormalities detected in any of the cultures examined. No cultures showed any sign of contamination by foreign algal cells or protozoa.

Measured concentrations of the active ingredient Phenothiol ranged from 80-93 % of nominal at 0 hours and 24-53 % at 72 hours. Measured concentrations in expired media were below 53 % probably due to the instability of test susbtance in aqueous media.

MCPA-thioethyl acid was inhibitory to the growth of *Selenastrum capricornutum* at concentrations in excess of 0.44 mg/L a.i.. The values for endpoints were as follows:

E_bC_{50} (72 h): 4.6 mg/L (95% confidence limits 3.8-5.5 mg/L) (0.92 mg a.i./l)

E_rC_{50} (0-72 h): 6.9 mg/L (95% confidence limits 6.3-7.6 mg/L) (=1.38 mg a.i./l)

NOEC: 2.2 mg/L (0.44 mg a.i./L)

Williams' test was used to compare the percentage inhibition in each treatment group with the baseline (control) values, to give the NOEC.

Study 2: Grunert B, 1991c (KCA 8.2.6/02)

The effects of Phenothiol (MCPA-thioethyl) (purity 93.4%) on algal growth of the aquatic plant *Scenedesmus subspicatus* after 72 h exposure was assessed in a static growth inhibition test as per GLP regulations and according to OECD guideline 201.

Triplicate flasks per concentration containing the green alga *Scenedesmus subspicatus* to a starting density of ca. 1.0 x 10^4 cells per mL, were tested to several concentrations of MCPA-thioethyl techincal compound. The flasks were incubated at 24 °C in an orbital shaker under continuous light at approximately 4300 lux and aliquots of the test solutions were removed at 24 hour intervals to determine the cell numbers. The following test concentrations were tested: 0, 0.009, 0.018, 0.036, 0.072, 0.144, 0.288, 0.575, 1.15, 2.3 mg/L MCPA-thioethyl. The results were expressed in terms of percentage of inhibition of the cell growth.

At the concentrations from 0.018 and 0.576 mg/L a stimulation of the cell growth versus the control was observed. At the concentrations from 0.036 to 0.288 mg/L MCPA-thioethyl a stimulation of growth rate in correlation with the control was observed. The concentration of 0.29 mg/L MCPA-thioethyl resulted in a 10% reduction of cell growth during a test period of 72 h. The concentration of 0.8 mg/L MCPA-thioethyl resulted in a 10% reduction of growth rate during a test period of 72 h. At test concentration of 0.009 mg/L (NOEC) neither a significant inhibition nor a significant stimulation of cell growth can be determined.
The concentration of MCPA-thioethyl which resulted in a 50% reduction of cell growth during a test period of 72 h (E_bC_{50} value) is greater than 2.3 mg/L (maximum solubility in water).

Study 3: Mantilacci S, 2014b (KCA 8.2.7/01)

The effects of the test item MCPA-thioethyl (Phenothiol (PHT)) (purity 99.0%) on vegetative growth of the aquatic plant *Lemna minor* after 7 days of exposure was assessed in a semi-static growth inhibition test, as per GLP regulations and according to OECD guideline 221. In this study, the test item is named as MCPA-thioethyl also known as Phenothiol (PHT).

A semi-static dose response test was conducted at 0.022, 0.070, 0.223, 0.713 and 2.280 mg/L of MCPA-thioethyl for 7 days. The test solutions were prepared in SIS medium by dilution of a stock solution of the test item in a solvent. One control series (CTRL SOLV) containing the solubilising agent at the maximum level used in treatments was run in addition to the treatment series.

The test samples were analysed according to the validated analytical method and the determination of the content of MCPA-thioethyl showed a mean recovery of 91.70% in the fresh samples and 66.63% in the spent samples.

The endpoints evaluation was performed using the geometric means of measured concentrations of MCPA-thioethyl.

The endpoints after 7 days growth based on the frond number evaluation were estimated to be the following:

- E_yC_{50}: 1.435 mg/L MCPA-thioethyl.
- NOE_rC and NOE_yC: 0.051 mg/L MCPA-thioethyl.

The growth inhibition observed at the highest test concentration (corresponding to the limit of solubility of MCPA-thioethyl in water) was lower than 50%, therefore the value of ErC_{50} was not statistically determinable.

The values for endpoints after 7 days growth based on the dry weight evaluation were estimated to be the following:

- E_yC_{50}: 1.935 mg/L MCPA-thioethyl;
- NOE_rC: 0.173 mg/L MCPA-thioethyl.
- NOE_yC: 0.051 mg/L MCPA-thioethyl.

The growth inhibition observed at the highest test concentration (corresponding to the limit of solubility of MCPA-thioethyl in water) was lower than 50%, therefore the value of ErC_{50} was not statistically determinable.

After 7 days of exposure, at the test concentration 0.713 and 2.280 mg/L (C4 and C5), some colonies had different appearance compared to the untreated cultures (some colonies appear smaller and deformed).

5.4.4 Other aquatic organisms (including sediment)

No additional data

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Aquatic Acute 1: H400: Very toxic to aquatic life M-factor = 10	Most sensitive species: 96 hr LC_{50} for trout (*O.mykiss*) 0.046 mg/L The lowest available $L(E)C_{50}$ value relevant for classification of MCPA-thioethyl is the 96 h LC_{50} of 0.046 mg a./L obtained for the fish – *O.mykiss*. Based on this lowest $L(E)C_{50}$ value MCPA-thioethyl fulfils the criteria L(C)E50 ≤ 1 mg/L for classification as Acute Aquatic Category 1, H400 (Very toxic to aquatic life) with M-factor of 10 due to 96 h LC_{50} in the range 0.01 < $L(E)C_{50}$ ≤ 0.1 mg/L.
Aquatic Chronic 1 H410: Very toxic to aquatic life with long lasting effects M-factor = 10	Most sensitive species: 21 day NOEC for *Daphnia magna* and 72 hour algal NOEC = 0.009 mg/L The lowest NOEC/EC_{10} is the 21 days NOEC of 0.009 mg a.i./L obtained for Daphnia magna and 72 hour algal NOEC of 0.009 mg a.i./L obtained for freshwater alga species Scenedesmus subspicatus. Available NOEC value for fish is higher. The lowest endpoint for MCPA-thioethyl fulfils the criteria NOEC/ECx ≤ 0.1 mg/L (for substance not readily biodegradable) for classification as Aquatic Chronic 1, H410 (Very toxic to the aquatic organisms with long lasting effects) with an M-factor of 10 due to the NOEC value in the range 0.001 mg/L < NOEC/ECx ≤ 0.01 mg/L (Table 4.1.3 of Annex I of CLP).

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

CLP: Aquatic Acute 1, H400 (M-factor 10);

Aquatic Chronic 1, H410 (M-factor 10)

6 OTHER INFORMATION

7 REFERENCES

Ahotupa M et al. (1983). Enhancement of extrahepatic drug metabolism by phenoxyacid herbicides and clofibrate. In: Rydsrom J et al., eds. Extrahepatic drug metabolism and chemical carcinogenesis. Elsevier Science Publishers BV, pp. 245–246.

Baldrick P. et al (1992): Twenty one dermal toxicity study in the rabbit with MCPA. Huntingdon Research Centre, Huntingdon, UK. Report No: 92/11896

Bell G (1995). Phenothiol 20% EC- Algal Growth Inhibition. Testing laboratory: Huntingdon Research Centre Ltd., P.O. Box2, Huntingdon, Cambridgeshire, PE18 6ES, England, Report No.: OXO 106A (a)/950946

Brekelmans MJC., (2003). Determination of the water solubility of Phenothiol at 3 pH values, NOTOX Report No 362969.

Bukowska B et al. (2000). Catalase activity in human erythrocytes: effect of phenoxyherbicides and their metabolites. Cell Biology International, 24(10):705–711.

Brunswik-Titze A (2015). Biodegradability in the CO2-evolution test according to OECD 301 B (July 1992). Testing laboratory: Hydrotox GmbH, Bötzinger Str. 29, 79111 Freiburg, Deutschland. Report no.: 930

Church S. 1984: Acute inhalation toxicity evaluation in rats 515-001, International Research & Development Corporation

Coggon D et al. (1986). Mortality of workers exposed to 2-methyl-4-chlorophenoxyacetic acid. Scandinavian Journal of Work, Environment & Health, 12:448–454.

DAR (2002): EU Draft Assessment Report, Annex B Volume 3 B.5 'Toxicology and Metabolism, MCPA TE (Phenothiol) Addendum', Italy August 2002

Dickhaus S. (1991a). Acute oral toxicological study of compound Phenothiol (tcn. act. agent) after one oral application to the rat. Testing laboratory: Pharmatox, Hannover, Germany. Report no.: 1-4-11-91.

Dickhaus S. 1991 (b): Acute oral toxicological study of compound Phenothiol (tcn.act.agent) after one oral application to the mouse, Pharmatox GmbH

Dickhaus S. (1991c). Acute toxicological study on compound Phenothiol (tcn. act. agent) after dermal application to the rat. Testing laboratory: Pharmatox, Hannover, Germany. Report no.: 1-4-13-9

Dickhaus S (1991d). Irritant effects of Phenothiol (tcn. act. agent) on rabbit skin acc. to Draize. Testing laboratory: Pharmatox, Hannover, Germany. Report no.: 1-3-14-91.

Dickhaus S. (1991e). Irritant effects of Phenothiol (tcn. act. agent) on rabbit eye. Testing laboratory: Pharmatox, Hannover, Germany. Report no.: 1-3-15-91

D'Olimpio, P. (2000). Surface tension of Phenothiol T.G. Centro Ricerche Novara "Istituto Guido Donegani" ENICHEM SpA). Report. 001/00

Duchnowicz P, Koter M, Duda W (2002). Damage of erythrocytes by phenoxyacetic acids and their metabolites. Pesticide Biochemistry and Physiology, 74:1–7.

Elo HA et al. (1991). Inhibition of human and rabbit platelet aggregation by chlorophenoxyacid herbicides. Archives of Toxicology, 65:140–144.

Flack I (1996). Phenothiol Physical and Chemical properties. Testing laboratory: Huntingdon Life Sciences Ltd., P. O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England.

Grunert B (1991a). Prolonged Toxicity Fish Test. Testing laboratory: BioChem, Dalmerstrasse 5b, 7500 Karlsruhe 21, Germany. Report no.: 91 20 43 023.

Grunert B (1991b). *Daphnia* Reproduction Test Phenothiol. Testing laboratory: BioChem, Dalmerstrasse 5b, 7500 Karlsruhe 21, Germany. Report no.: 91 20 43 023.

Grunert B (1991c). Alga, Growth Inhibition Test (OECD-Guideline 201) Phenthiol. Testing laboratory: BIoChem. Report no.: 912043023.

Harada T. (1992). Phenothiol: 18 months oral oncogenicity study in mice. Testing laboratory: The Institute of Envoronemntal Toxicology, Kodaura Laboratories. Report no.: IET 89-0077.

Hawkins T and Simmonds M (2015). [14C]-MCPA-thioethyl: Adsorption to and desorption from five soils. Testing laboratory: Battelle UK Ltd, 29 Springfield Lyons Approach, Chelmsford, Essex, CM2 5LB, United Kingdom. Report no.: VS/14/002.

Haynes LM (2015a). [14C]-MCPA-thioethyl Phototransformation of Chemicals in Water - Direct Photolysis. Testing laboratory: Battelle UK Ltd. 29 Springfield Lyons Approach Springfield Chelmsford, Essex, CM2 5LB, UK. Report no.: VS/14/003.

Haynes LM (2015b). [14C]-MCPA-thioethyl Indirect photolysis in natural water. Testing laboratory: Battelle UK Ltd. 29 Springfield Lyons Approach Springfield Chelmsford, Essex, CM2 5LB, UK. Report no.: VS/14/008.

Health Canada (2010) Guidelines for Canadian Drinking Water Quality: Guideline Technical Document 2-Methyl-4-chlorophenoxyacetic Acid (MCPA)

Hellwig J, Hildebrand B (1993a). Study of the prenatal toxicity of MCPA acid in rats after oral administration (gavage). Unpublished report no. 30R0374/91096 by BASF Aktiengesellschaft, Ludwigshafen, Germany.

Hellwig J, Hildebrand B (1993b). Study of the prenatal toxicity of MCPA acid in rabbits after oral administration (gavage). Unpublished report no. 40R0374/91095 by BASF Aktiengesellschaft, Ludwigshafen, Germany.

Hellwig J et al. (1992a). Preliminary study of the maternal toxicity of MCPA acid in rats after oral administration (gavage). Unpublished report no. 10R0374/91033 by BASF Aktiengesellschaft, Ludwigshafen, Germany.

Hellwig J et al. (1992b). Preliminary study of the maternal toxicity of MCPA acid in rabbits after oral administration (gavage). Unpublished report no. 20R0374/91063 by BASF Aktiengesellschaft, Ludwigshafen, Germany

Hietanen E et al. (1983). Effects of phenoxy herbicides and glyphosate on the hepatic and intestinal biotransformation activities in the rat. Acta Pharmacologica et Toxicologica, 53:103–112.

Hitchens J. and Frake E. (2014). MCPA-TE: Partition Coefficient n–Octanol/water (logPow) by HPLC Method (OECD 117), Report VS/14/007. Battelle UK Ltd.

Honda, H. (1998). Determination of physical-chemical properties of MCPA –thioethyl. Report No. 8F031G-8F036G. Mistsubishi Chemical Safety Institute

Inomata N et al. (1991a). Effects of ethyl 4-chloro-2-methylphenoxyacetic on hepatic peroxisomal enzymes in rats. Tohoku Journal of Experimental Medicine, 165(1):59–61.

Inomata N et al. (1991b). Effects of MCPA and other phenoxyacid compounds on hepatic xenophobic metabolism in rats. Tohoku Journal of Experimental Medicine, 165(3):161–173.

Irvine LFH (1980a). MCPA oral teratogenicity in the rat. Unpublished report no. 1996-277/7b by Hazleton Laboratories Europe, Harrogate, England.

Irvine LFH (1980b). MCPA oral teratogenicity in the Dutch Belted rabbit. Unpublished report no. 1737R-277/5 by Hazleton Laboratories Europe, Harrogate, England.

Irvine LFH, Tucker ML (1978a). MCPA oral teratogenicity dose ranging study in rats. Unpublished report no. 678R-277/6 by Hazleton Laboratories Europe, Harrogate, England.

Irvine LFH, Tucker ML (1978b). MCPA oral teratogenicity dose ranging study in rabbits. Unpublished report no. 684R-277/4 by Hazleton Laboratories Europe, Harrogate, England.

Itoh R., Toida S. 1974: Acute oral toxicity of Phenothiol. Department of Pharmacology, Faculty of Medicine Toho university

Johnson S, 2012 [14C]MCPA-thioethyl: In Vivo Kinetics Study in the Rat after Single Dosing Report number: VLB0003

JMPR (2012): MCPA 2012 JMPR Monograph. M. O'Mullane and A. Moretto, pp 653 – 724.

Juckeland D (2014). Acute toxicity of MCPA-thioethyl to the rainbow trout *Oncorhynchus mykiss* in a 96-hour semi-static test. Testing laboratory: BioChem agrar Labor für biologische und chemische Analytik GmbH Kupferstraße 6 04827 Gerichshain, Germany. Report no.: 14 10 48 004 W.

Kirsch P. et al (1985): Report on the study of the toxicity of MCPA in rats after 3-months administration in the diet. BASF Aktiengesellschaft, Ludwigshafen, Germany. Report No: 85/088

Kirsch P. et al (1988): Study on the chronic toxicity and oncogenic potential of MCPA in rats, administration in the diet over 24 months. BASF Aktiengesellschaft, Ludwighafen Germany. Report No: 88/0191

Kobayashi S. 1982: Skin and eye irritation studies with Phenothiol in rabbits. HOKKO Chem. Ind.

Kobayashi S. 1983: Report on the acute dermal toxicity with Phenothiol in rats. HOKKO Chem. Ind

Kondo J, Medical surveillance report (2002): Hokko Chemical Ind. Co. Ltd. , Tamano city, Okayama, Japan

Kühborth B et al. (1988). Study on the oncogenic potential of MCPA in mice, administration in the diet over 104 weeks. Unpublished report no. 80S0046/8358 by BASF Aktiengesellschaft, Ludwigshafen, Germany.

Kolmodin-Hedman B et al. (1983). Studies on phenoxy acid herbicides II. Oral and dermal uptake and elimination in urine of MCPA in humans. Archives of Toxicology, 54:267–273.

Lynge E et al. (1985). A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. British Journal of Cancer, 52:259–270.

MacKenzie K. (1986): Two generation reproduction study with MCPA in rats. Hazelton Laboratories America Inc, Madison, W I, USA. Report No: 86/420

Maita K. (1988). Phenothiol: 24-months oral chronic toxicity and oncogenicity study in rats. Testing laboratory: The Institute of Environmental Toxicology, Kodaira Laboratories. Report no.: Not given.

Maloney EK, Waxman DJ (1999). Trans-activation of PPARα and PPARγ by structurally diverse environmental chemicals. Toxicology and Applied Pharmacology, 161:209–218

Mantilacci S (2014a). Acute toxicity evaluation of MCPA-thioethyl on *Daphnia magna* in a 48-hours immobilization test under semi-static conditions. Testing laboratory: BioTecnologie B. T. Srl c/o

Parco Tecnologico Agroalimentare dell'Umbria Frazione Pantalla 06059 Todi (PG) ITALY. Report no.: BT019/14.

Mantilacci S (2014b). Toxicity evaluation of MCPA-thioethyl on *Lemna minor* in a semi-static growth inhibition test. Testing laboratory: BioTecnologie B. T. Srl c/o Parco Tecnologico Agroalimentare dell'Umbria Frazione Pantalla 06059 Todi (PG) ITALY. Report no.: BT020/14.

Mastalski K. (1976): Two-year chronic oral toxicity study with Phenothiol in beagle dogs. 651-05288 Industrial Bio-Test Laboratories Inc.

McDonald, A. 2014 [14C]MCPA-thioethyl: Distribution, Metabolism and Excretion Studies in the Rat after Single Dosing Report number: VLB0004

Meerts IATM. (2002). Micronucleus test in bone marrow cells of the mouse with MCPA-thioethyl. Testing laboratory: Notox, DL's-Hertogenbosch, The Netherlands. Report no.: 336241

Melkebeke T. *et al* (2002). The fate of Phenothiol in two water/sediment systems. Testing laboratory: NOTOX B. V., Hambakenwetering 7, 5231 DD's - Hertogenbosch, The Netherlands. Report no.: 336184.

Mellert W, Kaufmann W, Hildebrand B (1994a). MCPA-acid—Acute oral neurotoxicity study in Wistar rats. Unpublished report no. 20C0374/91106 by BASF Aktiengesellschaft, Ludwigshafen, Germany.

Mellert W et al. (1994b). MCPA-acid—Subchronic oral dietary toxicity and neurotoxicity study in Wistar rats. Unpublished report no. 50C0374/91133 by BASF Aktiengesellschaft, Ludwigshafen, Germany.

Milburn G (2004). 4-Chloro-2-methyl phenoxyacetic acid (MCPA): one generation study in the rat. Unpublished report no. RR1007 by Central Toxicology Laboratory, Alderley Park, England.

Mori V. (2015). MCPA-Thioethyl Active ingredient Surface Tension Research Center Biospheres study No. CPU-012-15

Morgan M. (1976). Three-generation reproduction study with Phenothiol in albino rats. Testing laboratory: Industrial Bio-test Laboratories Inc., Northbrook, Illinois, USA. Report no.: IBT 623-05289

Morrow L. (1974a). 90-day subacute oral toxicity study with Phenothiol in albino rats. Testing laboratory: Industrial Biotest Laboratories Inc., Northbrook, Illinois, USA. Report no.: 621-03772.

Morrow L. (1974 b): 90-day subacute oral toxicity study with Phenothiol in albino mice. 621-03773 Industrial Bio-test Laboratory Inc

Mulier B. (2003). Phenothiol technical: A 4-hour Acute inhalation toxicity study in the rat. Testing laboratory: RCC, Fullinsdorf and Itingen, Switzerland. Report no.: 846104

Mustonen R et al. (1989). Effects of commercial chlorophenolate, 2,3,7,8-TCDD, and pure phenoxyacetic acids on hepatic peroxisome proliferation, xenobiotic metabolism and sister chromatid exchange in the rat. Archives of Toxicology, 63:203–208.

Nagayoshi, E., (1999) Vapour pressure of MCPA-thioethyl. IET 98-5010-2. Institute Envir. Toxicology.

Odanaka Y (1999). Soil absorption/desorption of MCPA-thioethyl. Testing laboratory: The Institute of Environmental Toxicology (IET), Suzuki-cho 2-772, Kodaira-shi, Tokyo 187-0011, Japan. Report no.: IET-5010-5.

Pistl, J., et al. (1982) Determination of the immunotoxic potential of pesticides on functional activity of sheep leucocytes in vitro. Toxicology, 188:73-81

Reuzel P. et al (1980) Subchronic (13-week) oral toxicity study of MCPA in Beagle Dogs. TNO Central Inst. For Nutr. And Food Res. Zeist, Netherlands Report No: 80/0103

Roll R, Matthiaschk G. (1983): Vergleichende Untersuchungen zur Embryotoxizität von 2-Methyl-4-Chlorophenolessigsäure, Mecoprop und Dichlorprop bei NMRI Mäusen. Arznei. Forsch 33 Report No: 83/10103

Sakamaki S., Terazu M., Kurita N., Abo Y. Sugiya Y., 1985: Report on the teratology study in rabbits treated orally with Phenothiol. HO-541. Medical Scientific Research laboratory Omiya, Saitama, Japan. Report no.: HO-541

Slangen, P J., 2002, Aqueous hydrolysis of Phenothiol. NOTOX B. V., Hambakenwetering 7, 5231 DD ‘s-Hertogenbosch, The Netherlands. Report no.: NOTOX Report No. 336162

Shibuya T. (1984). Chromosome test of Phenothiol in Chinese Hamster V79 cells. Testing laboratory: Hatano Res. Institute, Food and Drug Saf. Center. Report no.: G-84-01CH

Shirasu Y., Noriya N., Kato K. (No date reported): Mutagenicity testing on Phenothiol in microbial systems Toxicology division, Institute Environmental Toxicology

Shirakawa M.(1973): Phenothiol: subchronic toxicity study in the mouse and rat for 3 months. Wakayama Medical College

Simmonds R (2015). [14C]-MCPA-thioethyl Aerobic mineralisation in surface water (OECD 309). Testing laboratory: Battelle UK Ltd. 29 Springfield Lyons Approach Springfield Chelmsford, Essex, CM2 5LB, UK. Report no.: VS/14/009

Sugiya Y. (1985). Dermal sensitization study with phenothiol technical in guinea pig. Testing laboratory: Medical Scientific Research Laboratory Co. Ltd., Saitama-Ken, Japan. Report no.: HO-5K01

Taino, G. (2015). Medical surveillance on manufacturing plant personnel, Statement: IRCCS Salvatore Maugeri Foundation, File number: AIIS3P5_9.

Tauchi K. (1984). Teratogenicity study of Phenothiol in the rat. Testing laboratory: Imamichi Institute for Animal Reproduction and Institute of Environmental Toxicology, Niihari-gun, Ibaraki, Japan. Report no.: IET 147.

Timchalk C (2004). 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, 200:1–19.

Verspeek-Rip CM. (2002). Evaluation of the mutagenic potential of MCPA-thioethyl in an in vitro mammalian cell gene mutation test with L5178Y mouse lymphoma cells. Testing laboratory: Notox, DL's-Hertogenbosch, The Netherlands. Report no.: 336239.

Wiklund K, Holm LE (1986). Soft tissue sarcoma risk in Swedish agricultural and forestry workers. Journal of the National Cancer Institute, 76:229–234.

Wiklund K, et al (1987). Risk of malignant lymphoma in Swedish pesticide appliers Br. J. Cancer 56 Report No: 87/10823

Willems H. (2003). Photodegradation of 14C-Phenothiol in water. Testing laboratory: NOTOX B. V., Hambakenwetering 7, 5231 DD 's-Hertogenbosch, The Netherlands. Report no.: NOTOX 361777.

Wonders J, Slangen PJ & van Noorloos B. (2002). Aqueous hydrolysis of Phenothiol at pH 4 and pH 7. Testing laboratory: NOTOX B. V., Hambakenwetering 7, 5231 DD 's-Hertogenbosch, The Netherlands. Report no.: NOTOX 357075

8 ANNEXES

IUCLID file.