Committee for Risk Assessment
RAC

Annex 1

Background document

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

dimethachlor (ISO); 2-chloro-*N*-(2,6-dimethylphenyl)-*N*-(2-methoxyethyl)acetamide

EC Number: 256-625-6
CAS Number: 50563-36-5

CLH-O-0000007432-78-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It is based on the official CLH report submitted to consultation and additional information (if applicable).

Adopted

14 March 2024

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European Commission

Draft Renewal Assessment Report prepared according to Regulation (EC) N° 1107/2009
and
Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N° 1272/2008

Dimethachlor (ISO); 2-chloro-*N*-(2,6-dimethylphenyl)-*N*-(2-methoxyethyl)acetamide

Volume 1

Rapporteur Member State: Croatia
Co-Rapporteur Member State: Austria

Version History

When	What
September 2021	First version submitted to EFSA
June 2022	Second version submitted to EFSA
January 2023	Third version submitted to ECHA
March 2023	Fourth version submitted to ECHA

Table of contents

Level 1

Dimethachlor

1 STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1.1 CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED

1.1.1 Purpose for which the draft assessment report was prepared

This Draft Renewal Assessment Report (DRAR) has been prepared in accordance with Commission Regulation (EC) No 844/2012 in order to evaluate the dossier submitted by Syngenta Crop Protection AG and to allow a decision on the renewal of the approval of the active substance dimethachlor.

This DRAR provides a discussion of relevant studies submitted for the original EU evaluation for Annex I inclusion as well as relevant new studies and information generated since the Annex I inclusion of dimethachlor in 2010. Where necessary, studies submitted for the original EU evaluation and re-evaluation for Annex I inclusion have been re-evaluated to allow risk assessment along current standards, and to validate previous conclusions and/or calculations.

Proposal for MRL setting was not included.

A proposal for Classification and Labelling is included within Volume 1.

1.1.2 Arrangements between rapporteur Member State and co-rapporteur Member State

According to Commission Regulation (EU) No 2016/183 Croatia was assigned Rapporteur Member State (RMS) and Austria assigned Co-Rapporteur Member State (Co-RMS).

Croatia acting as Rapporteur Member State (RMS) has evaluated all sections of the dossier. The draft Renewal Assessment Report (dRAR) was subjected to quality assurance by the Co-RMS Austria.

1.1.3 EU Regulatory history for use in Plant Protection Products

Dimethachlor is an existing active substance, the renewal of which is part of the AIR IV renewal programme.

During the previous evaluation dimethachlor was one of the 84 substances of the third stage Part B of the review programme covered by Commission Regulation (EC) No 1490/2002. Dimethachlor (CAS No 50563-36-5) was included on Annex I of 91/414/EEC on 01/01/10 under Inclusion Directive 2009/77/EC. Germany was the Rapporteur Member State (RMS). The date of expiration of approval is 31/12/2019 according to the Commission Implementing Regulation 540/2011/EC.

The following documents of the previous evaluation process resulting in the first approval of dimethachlor are considered to provide relevant review information on already accepted data or a reference to where such information and data can be found:

- Draft Assessment report on dimethachlor prepared by Germany (2007)
- Review report for the active substance dimethachlor Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 9 February 2009 in view of the inclusion of dimethachlor in Annex I of Directive 91/414/EEC - SANCO/177/08 – final 9 July 2010
- European Food Safety Authority (EFSA) - Conclusion regarding the peer review of the pesticide risk assessment of the active substance dimethachlor. EFSA Scientific Report (2008) 169, 1-111.
- COMMISSION DIRECTIVE 2009/77/EC of 1 July 2009 amending Council Directive 91/414/EEC to include chlorsulfuron, cyromazine, dimethachlor, etofenprox, lufenuron, penconazole, tri-allate and triflusulfuron as active substances

MRL

COMMISSION REGULATION (EC) No 149/2008 of 29 January 2008 amending Regulation (EC) No 396/2005 of the European Parliament and of the Council by establishing Annexes II, III and IV setting maximum residue levels for products covered by Annex I thereto
COMMISSION REGULATION (EU) 2018/78 of 16 January 2018 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for 2-phenylphenol, bensulfuron-methyl, dimethachlor and lufenuron in or on certain products

1.1.4 Evaluations carried out under other regulatory contexts

Dimethachlor is used only as herbicide and not regulated by other EU legislations (*e.g.* biocides, flavourings, food additives, cosmetics).
Dimethachlor was not included in the Inventory of Evaluations performed by the Joint Meeting on Pesticide Residues (JMPR).
FAO specification was not found.
The RMS did not find any evaluations of dimethachlor from US EPA nor PMRA, Canada.

1.2 APPLICANT INFORMATION

1.2.1 Name and address of applicant(s) for approval of the active substance

Name: Syngenta Crop Protection AG
Rosentalstrasse 67
4058 Basel
Switzerland

Contact: confidential information
Telephone number: confidential information
E-mail: confidential information

1.2.2 Producer or producers of the active substance

Name: Syngenta Crop Protection AG
Rosentalstrasse 67
4058 Basel
Switzerland

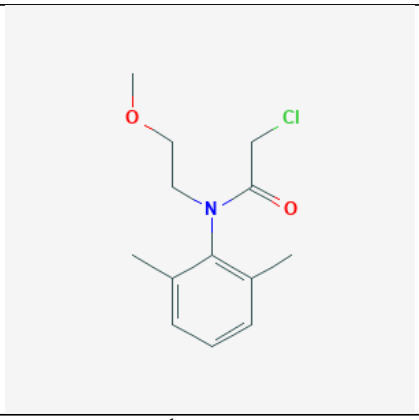
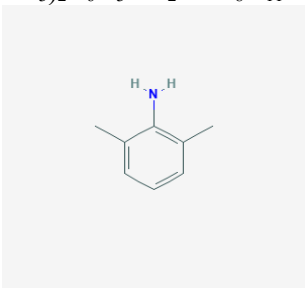
Contact: confidential information
Telephone number: confidential information
E-mail: confidential information

1.2.3 Information relating to the collective provision of dossiers

Syngenta Crop Protection AG is a sole applicant for renewal of the active substance dimethachlor.

1.3 IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1 Common name proposed or ISO-accepted and synonyms	dimethachlor (ISO); 2-chloro-*N*-(2,6 dimethylphenyl)-*N*-(2 methoxyethyl)acetamide, ISO: Dimethachlor
1.3.2 Chemical name (IUPAC and CA nomenclature)	

IUPAC	2-chloro-*N*-(2-methoxyethyl) acet-2′,6′-xylidide
CA	2-chloro-*N*-(2, 6-dimethylphenyl)-*N*-(2-methoxyethyl) -acetamide
1.3.3 Producer's development code number	CGA17020 or CGA017020
1.3.4 CAS, EEC and CIPAC numbers	
CAS	50563-36-5
EEC	256-625-6
CIPAC	688
1.3.5 Molecular and structural formula, molecular mass	
Molecular formula	$C_{13}H_{18}ClNO_2$
Structural formula	
Molecular mass	255.8 g mol^{-1}
1.3.6 Method of manufacture (synthesis pathway) of the active substance	CONFIDENTIAL information - data provided separately in Volume 4 for Syngenta
1.3.7 Specification of purity of the active substance in g/kg	Proposed purity: 950 g/kg
1.3.8 Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1 Additives	CONFIDENTIAL information - data provided separately in Volume 4 for Syngenta
1.3.8.2 Significant impurities	CONFIDENTIAL information - data provided separately in Volume 4 for Syngenta
1.3.8.3 Relevant impurities	CGA72649 Chemical name (IUPAC): 2,6-dimethylaniline CAS number: 87-62-7 Molecular formula: $(CH_3)_2C_6H_3NH_2$ or $C_8H_{11}N$ Structural formula:  Molecular mass: 121.18 g/mol Max. content: 0.5 g/kg
1.3.9 Analytical profile of batches	CONFIDENTIAL information - data provided

	separately in Volume 4 for Syngenta

1.4 INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1 Applicant	Syngenta Crop Protection AG Rosentalstrasse 67 4058 Basel Switzerland
1.4.2 Producer of the plant protection product	Syngenta Crop Protection AG Rosentalstrasse 67 4058 Basel Switzerland
1.4.3 Trade name or proposed trade name and producer's development code number of the plant protection product	TERIDOX 500 EC Code number: A5089H
1.4.4 Detailed quantitative and qualitative information on the composition of the plant protection product	
1.4.4.1 Composition of the plant protection product	Dimethachlor, 500 g/L
1.4.4.2 Information on the active substances	**Type** / **Name/Code Number** ISO common name: Dimethachlor (CGA 17020) CAS No: 50563-36-5 EC No: 256-625-6 CIPAC No: 688 Salt, ester anion or cation present: No
1.4.4.3 Information on safeners, synergists and co-formulants	CONFIDENTIAL information - data provided separately in Volume 4
1.4.5 Type and code of the plant protection product	Emulsifiable concentrate (EC)
1.4.6 Function	Herbicide
1.4.7 Field of use envisaged	Winter and spring oilseed rape
1.4.8 Effects on harmful organisms	Herbicide for pre-emergence or early post-emergence control of annual grasses and annual broadleaved weeds in winter or spring oilseed rape (in spring oilseed rape: pre-emergence only).

1.5 DETAILED USES OF THE PLANT PROTECTION PRODUCT

1.5.1 Details of representative uses

Crop and/or situation (a)	Member State	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (m)	Remarks
					Type (d-f)	Conc of a.i. g/kg (i)	Method kind (f-h)	Growth stage and season (j)	Number min max (k)	Interval between applications (min)	Kg a.i./hl min max (g/hl) (l)	Water l/ha min max	Kg a.i./ha min max (*) (g/ha) (l)		
Winter oilseed rape (BRSNN)	N-EU S-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 00-09 autumn	1	n/a	0,50	200	1,00	n/a	Only every third year on the same field. Pre-emergence use.
Winter oilseed rape (BRSNN)	N-EU S-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 10-20 autumn	1	n/a	0,50	200	1,00	n/a	Only every third year on the same field. Post-emergence use.
Winter oilseed rape (BRSNN)	N-EU S-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 00-09 autumn	1	n/a	0,33	300	1,00	n/a	Only every third year on the same field. Pre-emergence use.
Winter oilseed rape (BRSNN)	N-EU S-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 10-20 autumn	1	n/a	0,33	300	1,00	n/a	Only every third year on the same field. Post-emergence use.
Spring oilseed rape (BRSNN)	N-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual	EC	500 g/L	Broadcast spray application	BBCH 00-09 spring	1	n/a	0,50	200	1,00	n/a	Only every third year on the

				broadleaved weeds (TTTDS)										same field. Pre-emergence use.
Spring oilseed rape (BRSNN)	N-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 00-09 spring	1	n/a	0,33	300	1,00	n/a	Only every third year on the same field. Pre-emergence use.
Winter oilseed rape (BRSNN)	N-EU S-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 00-09 autumn	1	n/a	0,375	200	0,750	n/a	Only every third year on the same field. Pre-emergence use.
Winter oilseed rape (BRSNN)	N-EU S-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 10-20 autumn	1	n/a	0,375	200	0,750	n/a	Only every third year on the same field. Post-emergence use.
Winter oilseed rape (BRSNN)	N-EU S-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 00-09 autumn	1	n/a	0,25	300	0,750	n/a	Only every third year on the same field. Pre-emergence use.
Winter oilseed rape (BRSNN)	N-EU S-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 10-20 autumn	1	n/a	0,25	300	0,750	n/a	Only every third year on the same field. Post-emergence use.
Spring oilseed rape (BRSNN)	N-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual	EC	500 g/L	Broadcast spray application	BBCH 00-09 spring	1	n/a	0,375	200	0,750	n/a	Only every third year on the

				broadleaved weeds (TTTDS)										same field. Pre-emergence use.
Spring oilseed rape (BRSNN)	N-EU	TERIDOX 500 EC	F	Annual grasses (TTTMS) and annual broadleaved weeds (TTTDS)	EC	500 g/L	Broadcast spray application	BBCH 00-09 spring	1	n/a	0,25	300	0,750	n/a	Only every third year on the same field. Pre-emergence use.

(a) For crops, the EU and Codex classification (both) should be taken into account ; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and sucking insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes – GIFAP Technical Monograph N° 2, 1989
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant – type of equipment used must be indicated
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval

1.5.2 Further information on representative uses

The method of application: spray application using a hydraulic vehicle-mounted spray equipment.

Maximum number of applications and their timings: 1 application per crop/season. Total dose max. 1000 g dimethachlor/ha in a three-year period on the same field.

Water volume: 200-300 l/ha.

Growth stages of crops or plants to be protected: pre and post-emergence application (BBCH 00-09 or BBCH 10-20) for winter oilseed rape. Pre-emergence application (BBCH 00-09) for spring oilseed rape.

Development stages of the harmful organism concerned: pre-emergence and post-emergence.

Duration of protection afforded by each application and duration of protection afforded by the maximum number of applications: the application will protect the crop from annual grass and annual broadleaved weed competition up until it is harvested.

Minimum waiting periods or other precautions between last application and sowing or planting succeeding crops: there are no following crop restrictions within the context of a normal crop rotation.

Limitations on choice of succeeding crops: no restriction.

1.5.3 Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

Not relevant.

1.5.4 Overview on authorisations in EU Member States

A5089H, containing 500 g/L dimethachlor (trade name TERIDOX 500 EC)

Member state	Crop	Growth stage of crop	Max. number per crop/season	L product/ha	Kg a.i./ha	Remarks
Austria	winter oilseed rape	BBCH 00-09 (pre-em)	1	2	1	autumn application
Bulgaria	oilseed rape	BBCH 00-14	1	2	1	product can be applied once every 3 years
Croatia	oilseed rape	BBCH 00-09 or BBCH 12-14	1	2	1	Post-em application only in autumn. Product can be applied once every 3 years.
Czech Republic	oilseed rape		1	2	1	
Czech Republic	Silybum marianum (SLYMA)	BBCH 00-09 (pre-em)	1	2	1	not for human/animal uses
Czech Republic	Silybum marianum (SLYMA). Raphanus sativus subsp. oleiferus-seed prod.	BBCH 00-09 (pre-em)	1	2	1	not for human/animal uses
Estonia	winter oilseed rape	BBCH 00-09 or BBCH 10-14	1	2	1	product can be applied once every 3 years
Estonia	spring oilseed rape	BBCH 00-09 (pre-em)	1	2	1	product can be applied once every 3 years
France	winter oilseed rape	BBCH 00-08	1	1.5	0.75	product can be applied once every 3 years
Germany	winter oilseed rape	BBCH 00-09 or BBCH 10-14	1	2	1	
Hungary	winter oilseed rape	BBCH 00-09 (pre-em)	1	2	1	
Ireland	winter oilseed rape	BBCH 00-09 (pre-em)	1	2	1	
Latvia	winter and spring oilseed rape	BBCH 00-09 (pre-em)	1	2	1	product can be applied once every 3 years
Lithuania	winter oilseed rape	BBCH 00-14	1	2	1	
Lithuania	spring oilseed rape	BBCH 00-09 (pre-em)	1	2	1	

Poland	winter and spring oilseed rape	BBCH 00-09 (pre-em)	1	2	1	
Romania	oilseed rape	BBCH 00-09 or BBCH 10-16	1	2	1	product can be applied once every 3 years
Slovakia	winter oilseed rape	BBCH 00-09 (pre-em)	1	2.5	1.25	
Slovenia	oilseed rape	BBCH 00-09 (pre-em)	1	2	1	
United Kingdom	winter oilseed rape	BBCH 00-09 (pre-em)	1	2	1	

Level 2

Dimethachlor

2 SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

Summary of methodology proposed by the applicant for literature review and for all sections:

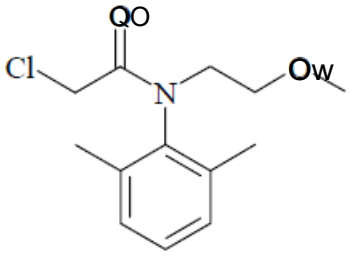
- A very broad search was conducted in a number of scientific source databases.
- Duplicates titles from within each database were automatically removed from the output.
- A rapid relevance assessment of the titles was conducted to remove any additional duplicates and any obviously irrelevant titles (where enough information was available from the title alone).
- Summary abstracts were requested for the remaining titles and a further rapid relevance assessment was conducted where again any clearly irrelevant titles were removed.
- A detailed assessment of the full-text documents for the remaining titles was conducted using the criteria developed for study relevance
- Any relevant papers were highlighted and assessed for reliability.

2.1 IDENTITY

2.1.1 Summary or identity

ISO common name: Dimethachlor
CAS No.: 50563-36-5
EEC/EINECS No.: 256-625-6
CIPAC No.: 688
IUPAC: 2-chloro-*N*-(2-methoxyethyl) acet-2′,6′-xylidide

CA: 2-chloro-N-(2, 6-dimethylphenyl)-N-(2-methoxyethyl)-acetamide
Structural Formula:



The purity of the active substance dimethachlor is proposed to stay the same as in original EU specification, 950 g/kg (dry weight), based on 5-batch analysis study from two manufacturing facilities. The active substance as manufactured contains one relevant impurity: 2,6-dimethylaniline.

2.2 PHYSICAL AND CHEMICAL PROPERTIES [EQUIVALENT TO SECTION 7 OF THE CLH REPORT TEMPLATE]

2.2.1 Summary of physical and chemical properties of the active substance

Table 1: Summary of physicochemical properties of the active substance

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3	EU agreed endpoint:	Das, 1994a	Visual pure substance:

Property	Value	Reference	Comment (e.g. measured or estimated)
kPa	Pure active substance: colourless crystals. Technical grade active substance: light beige waxy solid.	Das, 1995a	99.4% Technical substance: 96.8%
Melting/freezing point	EU agreed endpoint: 45.8 - 46.7°C	Das, 1994b	EEC A.1 (OECD 102) pure substance: 99.4%
Boiling point	EU agreed endpoint: The boiling point is approximately 320°C. Thermal decomposition starts at about 300°C.	Das, 1995b	EEC A.2 (OECD 103) pure substance: 99.4%
Relative density	-	-	-
Vapour pressure	EU agreed endpoint: 6.4 x 10^{-4} Pa at 20°C 1.5 x 10^{-3} Pa at 25°C **New study:** 2.3 x 10^{-3} Pa at 20°C 4.5 x 10^{-3} Pa at 25°C Proposed endpoint: 2.3 x 10^{-3} Pa at 20°C	Geoffroy, 1995 Vijayakumar, 2018	EEC A.4 pure substance: 99.4% OECD 104 pure substance: 99.5%
Surface tension	EU agreed endpoint: Surface tension of aqueous suspensions of technical grade dimethachlor at 20°C by the Wilhelmy plate method was determined to be: σ = 57.2 - 58.9 mN/m (filtrates of 1.9 g/L suspensions) σ = 66.1 - 67.0 mN/m (filtrates of 0.19 g/L suspensions) **New study and proposed endpoints:** The surface tension of a 1.0 g/L solution of dimethachlor PAI has been determined to be 56.8 mN/m at 20.0 +/- 0.5°C Pure dimethachlor is surface active with value lower than 60 mN/m.	Ryser, 1995 O'Connor B, 2016	OECD 115 ≅ EEC A.5 technical substance EEC A.5 pure substance 99.5%
Water solubility	EU agreed endpoint: 2.3 g/L at 25°C and pH 7 **New study:** 2.1 g/L at 20°C and pH 6.5 Proposed endpoint: 2.1 g/L at 20°C and pH 6.5	Stulz, 1994a Vijayakumar C, 2018	EEC A.6 pure substance: 99.4%EEC A.6 pure substance: 99.5%
Partition coefficient n-octanol/water	EU agreed endpoint: The octanol / water partition coefficient (P_{ow}) and its logarithm to base 10 (log P_{ow}) were determined to be: log P_{ow} = 2.17 ± (0.04) at 25°C.	Stulz, 1994b	EEC A.8 pure substance 99.4%

Property	Value	Reference	Comment (e.g. measured or estimated)
Henry's law constant	EU agreed endpoint: 1.7 x 10^{-4} Pa.m^3/mol at 25°C (based on Geoffroy, 1995) **New study:** 2.8 x 10^{-4} Pa.m^3/mol at 20°C (calculated from vapour pressure 2.3 x 10^{-3} Pa and water solubility 2.1 g/L, both measured at 20°C) Proposed endpoint: 2.8 x 10^{-4} Pa.m^3/mol at 20°C	Burkhard, 1996 Vijayakumar C., 2018	Calculation Calculation
Flash point	**New study and proposed endpoint:** 140 +/- 6°C Dimethachlor is not classified in terms of its flash point. The flash point is greater than 55°C.	Jackson, 2017	ASTM D3828 pure substance: 98.5%
Flammability	EU agreed endpoint: Dimethachlor is not considered highly flammable. **New study and proposed endpoint:** Not classified as a flammable solid	Schürch, 1995b Jackson, 2017	EEC A.10technical substance: 97.6% UN Test N.1 pure substance: 98.5%
Explosive properties	EU agreed endpoint: Dimethachlor is not considered an explosive substance **New study and proposed endpoint:** Dimethachlor is not an explosive substance	Schürch, 1995c Jackson, 2017	EEC A.14 technical substance: 97.6% ASTM E537 pure substance: 98.5%
Self-ignition temperature	EU agreed endpoint: Dimethachlor shows no self-ignition **New study and proposed endpoint:** Auto-ignition temperature: 465 +/- 25°C	Schürch, 1995d Jackson, 2017	EEC A.16 technical substance: 97.6% IEC 60079-20-1 pure substance: 98.5%
Oxidising properties	EU agreed endpoint: Dimethachlor is not considered an oxidizing substance. **New study and proposed endpoint:** Not an oxidizing substance	Schürch, 1995e Jackson, 2017	EEC A.17 technical substance: 97.6% UN Test O.2 pure substance: 98.5%
Granulometry	-	-	-

Property	Value	Reference	Comment (e.g. measured or estimated)
Solubility in organic solvents and identity of relevant degradation products	EU agreed endpoint: dichloromethane : > 500 g/L ethyl acetate : > 500 g/L methanol : > 500 g/L acetone : > 500 g/L n-octanol : 440 g/L toluene : > 500 g/L hexane : 42 g/LAll measured at 25ºC **New study and proposed endpoint:** dichloromethane : > 500 g/L ethyl acetate : > 500 g/L methanol : > 500 g/L acetone : > 500 g/L n-octanol : 310 g/L toluene : > 500 g/L hexane : 36 g/L Dichloromethane, ethyl acetate, methanol, acetone and toluene all at ambient temperature. Hexane and n-octanol at 20ºC	Stulz, 1995 Vijayakumar C, 2018	CIPAC MT 157.3 pure substance: 99.4% CIPAC MT 157.3 TGAI: 98.5%
Dissociation constant	EU agreed endpoint: Dimethachlor has no dissociation constant in an accessible pH range.	Jäkel, 1992	OECD 112 pure substance: 99.4%
Viscosity	Not relevant		

<table>
<tr><th>Property</th><th>Value</th><th>Reference</th><th>Comment (e.g. measured or estimated)</th></tr>
<tr><td>Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity</td><td>
EU agreed endpoint (new study for UV-VIS in neutral solution at 290 nm):

<u>Proton NMR</u>
H-NMR (250 MHz, $CDCl_3$)

<u>IR spectrometry</u>
FT-IR

<u>UV-VIS spectrometry</u>

Neutral solution: 1.2425 mg in 100 mL methanol; for 290 nm: 83.3 mg in 10 mL methanol

acidic solution: 1.2425 mg in 100 mL methanol / 1 N HCl (91+9)

basic solution: 1.2425 mg in 100 mL methanol / 1 N NaOH (91+9)

<table>
<tr><th>Solution</th><th>Wave length [nm]</th><th>ε [L/mol *cm]</th></tr>
<tr><td>Neutral</td><td>215</td><td>14461</td></tr>
<tr><td></td><td>265</td><td>486</td></tr>
<tr><td></td><td>290</td><td>3</td></tr>
<tr><td>Acidic</td><td>215</td><td>14768</td></tr>
<tr><td></td><td>265</td><td>572</td></tr>
<tr><td>Basic</td><td>219</td><td>9576</td></tr>
<tr><td></td><td>265</td><td>469</td></tr>
</table>
No significant absorption was observed between 290 nm and 750 nm.

<u>Mass spectrometry</u>
Mass spectrometry (EI and CI)

CGA72649:

<u>UV-VIS spectrometry</u>

Neutral solution: 1.75 mg in 100 mL methanol

Acidic solution: 1.75 mg in 100 mL methanol / 1 N HCl (91+9)

basic solution: 1.75 mg in 100 mL methanol / 1 N NaOH (91+9)

<table>
<tr><th>Solution</th><th>Wave length [nm]</th><th>ε [L/mol *cm]</th></tr>
<tr><td>Neutral</td><td>283.5</td><td>2000</td></tr>
<tr><td></td><td>233.5</td><td>7400</td></tr>
<tr><td>Acidic</td><td>270</td><td>300</td></tr>
</table>
</td><td>Oggenfuss P, 1999

Heintz K, 2014</td><td>OECD 101 pure substance: 99.4%

OECD 101pure substance: 99.5%

OECD 101
pure substance: 99.6%</td></tr>
</table>

Property	Value				Reference	Comment (e.g. measured or estimated)
			261.7	400		
		Basic	282.7	2000		
			231.4	7400		
	No significant absorption was observed between 340 and 750 nm. Mass spectrometry Mass spectrometry (EI and CI) Proton NMR H-NMR (250 MHz, $CDCl_3$) IR spectrometry FT-IR					

2.2.1.1 Evaluation of physical hazards [equivalent to section 8 of the CLH report template]

Dimethachlor is a colourless solid with a low melting temperature of 46°C. It is readily soluble in water and well soluble in most organic solvents, partition coefficient octanol/water log P_{OW} being 2.17 at 25°C. Its vapour pressure and volatility are low. Dimethachlor shows no hydrolysis under environmental conditions and is stable to photolysis too. The technical material is not explosive, has no auto-ignition temperature and does not burn under test conditions.

Based on the studies provided for the Annex I inclusion and renewal of active substance, it can be concluded following:
Dimethachlor does not meet the criteria for classification as an explosive because it has no reactive functional group, it has exothermic decomposition energy of less than 500 J/g and oxygen balance calculation does not trigger criteria for explosive properties. Regarding the classification as flammable solid, self-reactive substance, phyrophoric solid and self-heating substance, provided studies demonstrate no classification required since the data is not sufficient for classification.

2.2.1.1.1 Explosives *[equivalent to section 8.1 of the CLH report template]*

Table 2: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
EEC A.14	Dimethachlor is not an explosive substance.	97.6% TGAI	Schürch, 1995c
ASTM E537	Dimethachlor is not an explosive substance.	98.5% PAI	Jackson, 2017

2.2.1.1.1.1 Short summary and overall relevance of the provided information on explosive properties

Dimethachlor is not considered an explosive, as concluded from the test results on thermal sensitivity (effect of flame), mechanical sensitivity (shock and friction) and differential scanning calorimetry. The screening procedure has not identified the presence of any reactive chemical group and the potential for rapid energy release. Results of the provided test methods rule out explosive properties as results of ASTM E537 method show that the exothermic decomposition energy is less than 500 J/g. Based on the performed calculation formula the oxygen balance is less that -200 (-206.5) and with that calculation it can be concluded that the dimethachlor molecule is not explosive.

2.2.1.1.1.2 Comparison with the CLP criteria

Not explosive according to the CLP criteria.
As stated in Annex I part 2 point 2.1.4.3 of Regulation (EC) No. 1272/2008: “A substance or mixture shall not be classified as explosive if:

(a) There are no chemical groups associated with explosive properties present in the molecule. Examples of groups which may indicate explosive properties are given in Table A6.1 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria".
As there are no functional groups associated with explosive properties in the molecule no classification is warranted.
After performed tests and based on the acceptance procedure as stated in Annex I part 2 point 2.1.4.1 of Regulation (EC) No. 1272/2008 it can be concluded that dimethachlor is not explosive.

2.2.1.1.1.3 Conclusion on classification and labelling for explosive properties

Dimethachlor does not meet the criteria for classification as an explosive.

2.2.1.1.2 Flammable gases (including chemically unstable gases) ***[equivalent to section 8.2 of the CLH report template]***

Not applicable.

2.2.1.1.2.1 Short summary and overall relevance of the provided information on flammable gases (including chemically unstable gases)

Not applicable.

2.2.1.1.2.2 Comparison with the CLP criteria

Not applicable.

2.2.1.1.2.3 Conclusion on classification and labelling for flammable gases

Not applicable.

2.2.1.1.3 Oxidising gases ***[equivalent to section 8.3 of the CLH report template]***

Not applicable.

2.2.1.1.4 Gases under pressure ***[equivalent to section 8.4 of the CLH report template]***

Not applicable.

2.2.1.1.5 Flammable liquids ***[equivalent to section 8.5 of the CLH report template]***

Not applicable.

2.2.1.1.6 Flammable solids ***[equivalent to section 8.6 of the CLH report template]***

Table 3: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
EEC A.10	Dimethachlor is not considered highly flammable	technical substance: 97.6 %	Schürch, 1995b
UN Test N.1	Not classified as a flammable solid	pure substance: 98.5 %	Jackson, 2017

2.2.1.1.6.1 Short summary and overall relevance of the provided information on flammable solids

A flame of a gas burner resulted in melting of the substance. Dimethachlor did not catch fire, neither melted and unmelted. It did not propagate combustion. Dimethachlor is not considered as highly flammable.

2.2.1.1.6.2 Comparison with the CLP criteria

Not flammable according to the CLP criteria.

2.2.1.1.6.3 Conclusion on classification and labelling for flammable solids

Dimethachlor does not meet the criteria for classification as flammable.

2.2.1.1.7 Self-reactive substances *[equivalent to section 8.7 of the CLH report template]*

Table 4: Summary table of studies on self-reactive substances

Method	Results	Remarks	Reference
EEC A.10 EEC A.16	Dimethachlor shows no self-ignition	technical substance: 97.6 %	Schürch, 1995e
IEC 60079-20-1	Auto-ignition temperature: 465 ± 25 °C, no self-ignition	Pure substance: 98.5 %	Jackson, 2017

2.2.1.1.7.1 Short summary and overall relevance of the provided information on self-reactive substances

Dimethachlor does not self-ignite with respect of melting point or prior to the temperature which is end-point of the test (465±25 °C).

2.2.1.1.7.2 Comparison with the CLP criteria

According to the Annex I part 2 point 2.8.4.2 of Regulation (EC) No. 1272/2008: *"The classification procedures for self-reactive substances and mixtures need not be applied if:*
(a) There are no chemical groups present in the molecule associated with explosive or self reactive properties. Examples of such groups are given in Tables A6.1 and A6.2 in Appendix 6 of the UN RTDG Manual of Tests and Criteria.
As there are no functional group associated with self-reactive properties in the molecule, no classification procedure shall be applied.

2.2.1.1.7.3 Conclusion on classification and labelling for self-reactive substances

Dimethachlor does not meet the criteria for classification as self-reactive substance. Data conclusive but not sufficient for classification.

2.2.1.1.8 Pyrophoric liquids *[equivalent to section 8.8 of the CLH report template]*

Not relevant.

2.2.1.1.9 Pyrophoric solids *[equivalent to section 8.9 of the CLH report template]*

Table 5: Summary table of studies on phyrophoric solids

Method	Results	Remarks	Reference
EEC A.10 EEC A.16	Dimethachlor shows no self-ignition	technical substance: 97.6 %	Schürch, 1995e
IEC 60079-20-1	Auto-ignition temperature: 465 ± 25 °C, no self-ignition	Pure substance: 98.5 %	Jackson, 2017

2.2.1.1.9.1 Short summary and overall relevance of the provided information on phyrophoric solids

Dimethachlor does not self-ignite with respect of melting point or prior to the temperature which is end-point of the test (465±25 °C). Based on the provided studies and relevant data over the years of use of dimethachlor it can be concluded that it is not phyrophoric.

2.2.1.1.9.2 Comparison with the CLP criteria

According to the Annex I part 2 point 2.10.4.1 of Regulation (EC) No. 1272/2008: *"The classification procedure for pyrophoric solids need not be applied when experience in manufacture or handling shows that the substance*

or mixture does not ignite spontaneously on coming into contact with air at normal temperatures." No classification required.

2.2.1.1.9.3 Conclusion on classification and labelling for phyrophoric solids

Dimethachlor does not meet the criteria for classification as phyrophoric solids. Data conclusive but not sufficient for classification.

2.2.1.1.10 Self-heating substances *[equivalent to section 8.10 of the CLH report template]*

Table 6: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
EEC A.10 EEC A.16	Dimethachlor shows no self-ignition	technical substance: 97.6 %	Schürch, 1995e
IEC 60079-20-1	Auto-ignition temperature: 465 ± 25 °C, no self-ignition	Pure substance: 98.5 %	Jackson, 2017

2.2.1.1.10.1 Short summary and overall relevance of the provided information on self-heating substances

The test was carried out in accordance with IEC 60079-20-1, Section 7, "Method of Test for Auto-Ignition Temperature", but with 5°C temperature increments rather than the specified 2°C increments. The tests are carried out at different temperatures, using a range of sample quantities, in order to establish the lowest temperature at which auto-ignition occurs for any sample quantity. The final confirmatory tests to establish the ignition/no ignition temperatures are made at 5°C increments, using maximum observation periods of 5 minutes. Dimethachlor not considered self-heating or self-igniting.
Results of the screening criteria which is melting point below 160 °C (45.8 - 46.7°C) are in accordance with data provided.

2.2.1.1.10.2 Comparison with the CLP criteria

According to the Annex I part 2 point 2.11.4.2 of Regulation (EC) No. 1272/2008: "The classification procedure for self-heating substances or mixtures need not be applied if the results of a screening test can be adequately correlated with the classification test and an appropriate safety margin is applied." EU test method A.16 as described in Regulation (EC) No 440/2008 checks for self-heating properties.
Results of the EEC method A16show that no classification for dimethachlor is required.

2.2.1.1.10.3 Conclusion on classification and labelling for self-heating substances

Dimethachlor does not meet the criteria for classification as self-heating. Data conclusive but not sufficient for classiffication.

2.2.1.1.11 Substances which in contact with water emit flammable gases *[equivalent to section 8.11 of the CLH report template]*

According to the Annex I part 2 point 2.12.4.1 of Regulation (EC) No. 1272/2008: "The classification procedure for this class need not be applied if: (a) the chemical structure of the substance or mixture does not contain metals or metalloids".

As there are no metals or metalloids present in the molecule, it can be concluded that dimethachlor is not to be considered as substance which in contact with water emit flammable gas.

2.2.1.1.12 Oxidising liquids *[equivalent to section 8.12 of the CLH report template]*

Not applicable.

2.2.1.1.13 Oxidising solids *[equivalent to section 8.13 of the CLH report template]*

Table 7: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
EEC A.17	Dimethachlor is not considered an oxidizing substance.	technical substance: 97.6 %	Schürch, 1995e
UN Test O.2	Not an oxidizing substance	Pure substance: 98.5 %	Jackson, 2017

2.2.1.1.13.1 Short summary and overall relevance of the provided information on oxidising solids

Dimethachlor and cellulose was mixed in different ratios and ignited. It should be noted that method used was UN Test O.2 which is relevant for oxidising liquids, and not solids. Since the substance as technical material can be present in the form of liquid (i.e. solvent based technical concentrate), it can be relevant for usid test method UN Test O.2. No evidence of oxidizing properties was observed. Dimethachlor contains oxygen but it is bonded to carbon only, therefore the oxidising properties are predicted negative.

2.2.1.1.13.2 Comparison with the CLP criteria

Not an oxidising solid according to the CLP criteria. According to the Annex I part 2 point 2.14.4.1 of Regulation (EC) No. 1272/2008: "For organic substances or mixtures the classification procedure for this class shall not apply if:
(a) the substance or mixture does not contain oxygen, fluorine or chlorine; or
(b)the substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen."
As dimethachlor contains oxygen but it is chemically bondend only to carbon, it is not to be considered for classification in this hazard class.

2.2.1.1.13.3 Conclusion on classification and labelling for oxidising solids

Dimethachlor does not meet the criteria for classification as an oxidising substance. Data conclusive but not sufficient for classification.

2.2.1.1.14 Organic peroxides *[equivalent to section 8.14 of the CLH report template]*

Dimethachlor does not contain the bivalent organic peroxide –O-O structure. According to the Annex I part 2 point 2.15.1.1 of Regulation (EC) No. 1272/2008: "Organic peroxides means liquid or solid organic substances which contain the bivalent -O-O- structure" As none of SCLPs (acetates, alcohols, aldehydes and blends) contain the bivalent O-O- structure, they are not to be considered for classification in this hazard class.

Data conclusive but not sufficient for classification.

2.2.1.1.15 Corrosive to metals *[equivalent to section 8.15 of the CLH report template]*

No studies submitted. Based on all other relevant data it can be concluded that it data is conclusive but not sufficient for classification.

2.2.2 Summary of physical and chemical properties of the plant protection product

The product A5089H is an emulsifiable concentrate (EC). The appearance of the product is that of clear, brown liquid with a thymol like odour. It is not explosive, not oxidising and not highly flammable. It has a self ignition temperature of 450 °C and a flash point of 65 °C. It has a pH value of 5.3 (1% in water) and the surface tension of the undiluted product (34.4 mN/m) and aqueous dilutions of the product, indicates that is surface active. Furthermore, considering hydrocarbons content (> 10%) in the preparation and the kinematic viscosity (7.01 mm²/s at 40 °C), this product is classified H304 Cat.1, but not R65.
There is no effect of high temperature on the stability of the formulation, since after 14 days at 54 °C in HDPE/PA container, neither the active ingredient content nor technical properties were changed. However, in the cold stability study, after storage for 7 days at 0 °C and after standing 24 hours at room temperature, crystals were observed. Further low temperature stability tests were carried out using formulation material stored at 10°C for 7 days; the results demonstrated that no crystals formed and the emulsion stability was acceptable. **As a consequence it is recommended to protect the preparation from frost.**

In the emulsion stability test at the concentration of 0.5 % in CIPAC water D at 30 °C, the re-emulsification after 24 hours was not complete. In order to investigate the emulsion properties further towards more realistic application conditions, the test temperature was modified to 20 °C. At this temperature, the re-emulsifiability was found to be complete. These findings demonstrate that the formulation can be completely and easily re-dispersed by means of gentle agitation (10 inversions of the test cylinder) at a temperature closer to practical application conditions (20 °C).Therefore, A5089H can be applied safely and uniformly under practical application conditions in the field.
Emulsion stability data after 2 weeks at 54 °C storage show that formulation should be shaken before use to homogenize the preparation, and shaken during use, in compliance with good agricultural practices recommendations.
The stability data indicate a shelf life of at least two years at ambient temperature provided the product is stored in an unopened original f-HDPE and HDPE-PA container, away from direct sunlight and kept at a temperature above 10 °C throughout transport and storage.

The technical characteristics of A5089H are acceptable for an EC formulation.

2.3 DATA ON APPLICATION AND EFFICACY

2.3.1 Summary of effectiveness

Oilseed rape may be infested by a rich and varied weed flora germinating in late summer, in autumn or spring. Different grass and broadleaved weeds compete with oilseed rape for space, light and nutrients from early stages of development. They cause substantial yield losses and influence its quality. The induced reduction on yield depends on the weed species, the weeds density, the length of the period of competition and the availability of water and nutrients.

Dimethachlor is an herbicide recommended as pre-emergence or early post-emergence treatment for the control of annual grasses and annual broadleaved weeds in winter or spring oilseed rape (in spring oilseed rape: pre-emergence only).

The major grass and broadleaved weeds on which dimethachlor has activity are:
Apera sp., *Lolium rigidum* and *multiflorum*, *Poa annua, Anagallis* sp., *Anthemis arvensis*, *Atriplex patula*, *Capsella bursa-pastoris*, *Cerastium glomeratum, Fumaria* sp., *Galeopsis* sp., *Lamium* sp., *Lapsana communis, Matricaria* sp., *Mercurialis annua, Myosotis arvensis*, *Rumex* sp., *Senecio vulgaris*, *Solanum nigrum*, *Sonchus* sp., *Stellaria media*, *Veronica* sp.

2.3.2 Summary of information on the development of resistance

Dimethachlor is classified according to its mechanism of action (inhibition of cell division, inhibition of very long chain fatty acids) in group 15 (chloroacetamide family) of the Herbicide Resistance Action Committee (HRAC) (http://www.weedscience.org).
A5089H is an emulsifiable concentrate formulation (EC) containing 500 g dimethachlor/L. The claimed application rate is up to 2 L/ha on the same field maximum every three years. The product is widely used in oilseed rape for many years.

Resistance development: According to Ian Heap's website, no cases of weed resistance to dimethachlor are documented from Europe (http://www.weedscience.org). So, no natural resistance mechanisms are known against dimethachlor.

Weed sensitivity: The weed spectrum of dimethachlor against annual grasses and annual broadleaved weeds is described above. To complement the spectrum of weeds controlled, A5089H is often used together with other herbicides with different modes of action as tank mix applications or spray programs.

Risk of resistance development: Chloracetamides, including dimethachlor, are widely used for many years. A5089H is used as single treatment only for weed control in oilseed rape. Commission Implementing Regulation (EU) No 540/2011 limits the application of dimethachlor to once every three years on the same field. To broaden the spectrum against broadleaved weeds, A5089H is also often tank mixed with partner herbicides with different modes of action.

Therefore, the selection pressure as a result of practical use of A5089H and the risk of weed resistance developing to dimethachlor, can be judged as low.
Other chloracetamides belonging to the same mode of action group are used mainly in maize. However, maize is very rarely planted in the crop rotation before or after oilseed rape. In crops in which other chloracetamides are used (metolachlor or metazachlor) and in oilseed rape, an additional post-emergence grass herbicides with a different mode of action (acetyl-CoA carboxylase inhibitors) are often used for additional control of grass weeds, including volunteer cereals.

Overall it can be concluded that the risk of resistance development to A5089H is low.

2.3.3 Summary of adverse effects on treated crops

Dimethachlor has been applied in many EU member states for many years without reports of phytotoxic effects on treated or succeeding crops. Consequently, no negative impact is expected on treated crops when used according to the label recommendations.

2.3.4 Summary of observations on other undesirable or unintended side-effects

There is no evidence of any undesirable or unintended side-effects. Years of commercial uses have demonstrated that dimethachlor, when used according to the label recommendations, does not induce any particular undesirable effects.

2.4 FURTHER INFORMATION

2.4.1 Summary of methods and precautions concerning handling, storage, transport or fire

A5089H

Requirements for storage areas and containers:
No special storage conditions required.
Keep containers tightly closed in a dry, cool and well-ventilated place.
Keep out of the reach of children.
Keep away from food, drink and animal feeding stuffs.

Advice on safe handling:
No special protective measures against fire required.
Avoid contact with skin and eyes.
When using do not eat, drink or smoke.

Transport:
Land transport
ADR/ RID:

UN-Number:	3082
Transport hazard class:	9
Classification code:	M6
Labels:	9
Packaging group	III
Proper shipping name:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (DIMETHACHLOR)

Sea transport
IMDG:

UN-Number:	3082
Transport hazard class:	9
Classification code:	M6
Labels:	9
Packaging group:	III

Proper shipping name:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (DIMETHACHLOR)

Air transport
IATA-DGR

UN-Number:	3082
Transport hazard class:	9
Labels:	Miscellaneous
Packaging group:	III
Proper shipping name:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (DIMETHACLOR)

Fire
Suitable extinguishing media:
Extinguishing media - small fires: Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Extinguishing media - large fires: Use alcohol-resistant foam or water spray.
Extinguishing media which shall not be used for safety reasons: Do not use a solid water stream as it may scatter and spread fire.

Specific hazards during fire fighting: As the product contains combustible organic components, fire will produce dense black smoke containing hazardous products of combustion. Exposure to decomposition products may be a hazard to health.
Special protective equipment for firefighters: Wear full protective clothing and self-contained breathing apparatus.
Further information minimise the hazards arising: Do not allow run-off from fire-fighting to enter drains or water courses. Cool closed containers exposed to fire with water spray.
Hazardous decomposition products likely to be generated in the event of fire: Combustion or thermal decomposition will evolve toxic and irritant vapours.
Hazardous reactions: No dangerous reaction known under conditions of normal use.

2.4.2 Summary of procedures for destruction or decontamination

Empty remaining contents.
Triple rinse containers.
Empty containers should be taken to an approved waste handling site for recycling or disposal.
Do not re-use empty containers.
If the product contaminates rivers and lakes or drains inform respective authorities.
Do not contaminate ponds, waterways or ditches with chemical or used container.
Do not dispose of waste into sewer.
Where possible recycling is preferred to disposal or incineration.
If recycling is not practicable, dispose of in compliance with local regulations.
As the halogen content of A5089H is below the 60% trigger value, high temperature incineration is the preferred means of disposal for the active substances, formulated products, contaminated materials or contaminated packaging. Incineration should be carried out in a licensed incinerator operating at a temperature above 800°C and with a minimum gas phase residence time of two seconds.

2.4.3 Summary of emergency measures in case of an accident

In the event of accidental spillage, contain spillage, and then collect with non-combustible absorbent material (e.g. sand, earth, diatomaceous earth, vermiculite) and place in container for disposal according to local/national regulations. Prevent further leakage or spillage if safe to do so. Do not flush into surface water or sanitary sewer system.

First aid measures

General advice:

Have the product container, label or Material Safety Data Sheet with you when calling the Syngenta emergency number, a poison control centre or physician, or going for treatment.
Inhalation:
Immediately move to fresh air. If breathing is irregular or stopped, administer artificial respiration. Keep patient warm and at rest. Call a physician or Poison Control Centre immediately.
Skin contact:
Take off all contaminated clothing immediately. Wash off immediately with plenty of water. If skin irritation persists, call a physician. Wash contaminated clothing before re-use.
Eye contact:
Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Remove contact lenses. Immediate medical attention is required.
Ingestion:
If swallowed, seek medical advice immediately and show this container or label. Do NOT induce vomiting: contains petroleum distillates and/or aromatic solvents.
Medical advice:
Aspiration may cause pulmonary oedema and pneumonitis. There is no specific antidote available. Treat symptomatically.

2.5 METHODS OF ANALYSIS

2.5.1 Methods used for the generation of pre-authorisation data

Analysis of the active substance as manufactured

Analytical method **AWA-30/1** has been developed for the determination of the pure active substance, dimethachlor (CGA017020) in the active substance as manufactured (**80 % solution in cyclohexanone**). Determination of the active substance dimethachlor (CGA017020) by gas chromatography and flame ionization detection (GC/FID). Quantification is achieved by comparison of the peak area to that of the reference solution with a concentration of 1 mg/mL CGA017020. Reference substances of known quality served as the external standard. Validation is acceptable, and the method is suitable for the determination of dimethachlor in technical dimethachlor as manufactured.

Analytical method **AW-30/3** has been developed for the determination of the pure active substance, dimethachlor (CGA017020) in the active substance as manufactured (**solvent-free grade**). Determination of the active substance dimethachlor (CGA017020) by gas chromatography and flame ionization detection (GC/FID). Quantification is achieved by comparison of the peak area to that of a reference solution with a concentration of 1 mg/mL CGA017020. Reference substances of known quality served as the external standard. Validation is acceptable, and the method is suitable for the determination of dimethachlor in technical dimethachlor as manufactured.

Formulation analysis

The HPLC method **SF-480/1** was employed for the determination of dimethachlor in formulation TERIDOX EC 500. Dimethachlor is determined in A5089H by liquid chromatography on a reversed phase column, using 0.1% phosphoric acid, acetonitrile as eluent, and UV detection at 240 nm. Quantification was by comparison of peak area ratios to that of a reference solution. The validation of the method is acceptable and in accordance with SANCO/3030/99 rev.4.

A5089H contains the active substance dimethachlor that contains the relevant impurity CGA72649 (2,6-dimethylaniline) with maximum allowed content of 0.5 g/kg. Analytical Method **SD-1745/1**: Determination of Dimethachlor Relevant Impurity CGA72649 in formulation by GC/MS/MS, was developed using standard addition sample preparation coupled with gas chromatography with mass spectroscopy detection. Quantification is conducted by reference to a multiple point linear calibration i.e. area count vs. concentration of CGA72649. Validation of the method is acceptable.

2.5.2 Methods for post control and monitoring purposes

Adequate methods are available to monitor the respective current residue definition in plant material, soil, drinking water, surface water and air. A summary of adequate enforcement methods are given in the tables below:

Matrix group / crop group	Residue definition for monitoring	LOQ	Methods		
			Primary method	**Confirmatory method**	**Independent lab validation**
Lettuce = Commodity with high water content Oilseed rape seed = Commodity with high oil content Dried broad beans = Commodity with high protein content Cereal grain = Dry commodity (high starch content) Whole orange = Commodity with high acid content	Dimethachlor	0.01 mg/kg each	**Heinz N.; 2019; P 5074 G** QuEChERS method CGA017020_10370 LC-MS/MS Dimethachlor two transitions	**not necessary**	**Hillier K.; 2019 CS84KW** LC-MS/MS covering two crop groups (oilseed rape seed and tomato)
Blood Liver Milk Eggs Muscle Fat	Not required	0.01 mg/kg each	**Watson G., 2019; RES-00177** QuEChERS method CGA017020_10354 LC-MS/MS two transitions for dimethachlor and CGA048083 (for blood and liver only)	**not necessary** for dimethachlor and CGA048083	**Hillier K., (2019a)** QK48RS LC-MS/MS covering three animal matrices (egg, liver and milk)
Soil	Dimethachlor, SYN530561, CGA42443, CGA50266, CGA102935, SYN547047, CGA354742 CGA369873 and CGA373464	0.001 mg/kg	**Bodsch J. and Wenner O.; 2019** GRM008.11A LC-MS/MS two transitions CGA017020_10368	**Bodsch J. and Wenner O.; 2019a** IF-18/04474866 LC-MS/MS two transitions CGA017020_10377	**Not necessary**
Water (surface)	Dimethachlor, SYN530561, CGA42443,	0.05 µg/L	**Braid S., Asuncion L. and Amic S.,**	**Amic S., 2016a S14-05396** LC-MS/MS	**Andre, M.; 2017, IF-**

Matrix group / crop group	Residue definition for monitoring	LOQ	Methods		
			Primary method	**Confirmatory method**	**Independent lab validation**
	CGA37734, CGA50266, CGA102935, SYN547047, CGA39981, CGA354742 CGA369873 and CGA373464		**2016, GRM008.05A** LC-MS/MS two transitions **CGA017020_10212**	two transitions with exception metabolite CGA50266 (1 primary and 2 confirmatory transitions) CGA017020_10208	**16/03930421-FIN** LC-MS/MS two transitions with exception metabolite CGA50266 (1 primary and 2 confirmatory transitions) CGA017020_10241
Air	Dimethachlor	1.0 µg/m^3	**Hargreaves S.L.; 2006; RAM 484/01** LC-MS/MS CGA17020/0770 3 daughter ions m/z= 256	**Evans P.G.; 2006; RJ3754B** CGA17020/0769 **(not necessary)**	**Not necessary**

2.6 EFFECTS ON HUMAN AND ANIMAL HEALTH

More detailed results of the studies are presented in Volume 3, section B.6.

2.6.1 Summary of absorption, distribution, metabolism and excretion in mammals *[equivalent to section 9 of the CLH report template]*

Table 8: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Absorption, distribution, degradation, and excretion study in the rat. OECD 417 (1984). Oral (gavage) Rat Tif: RAIf (SPF) 5 M, 5F (ADME) 4 M, 4F (blood levels) 9M, 9 F (tissue levels) 6 M (excretion low dose) 4 M (excretion highdose) [U-^{14}C]phenyl 2-chloro-N-(2,6-dimethylphenyl)-N-(2-methoxyethyl)-acetamide (radioactive dimetachlor - CGA 17020) single doses of 0,5 and 100 mg/kg bw Vehicle: PEG 200/ethanol/water (1:1:2, v/v). 7 days observation, 30 days for blood level groups	A: Complete absorption of the test substance. D: The highest tissue residues were found in whole blood. Consequently, organs highly perfused with blood showed rather high residues (lungs, heart, kidneys, liver, spleen). The depletion from the tissues appears to follow monophasic first order kinetics. The half-life times ($t_{1/2}$) were generally in the range of 10 to 30 days. The long half-life is a consequence of covalent binding to haemoglobin (rat specific). M: The metabolite pattern determined in urine, faeces, and bile samples demonstrated that essentially 100% of the orally administered dimethachlor were degraded. TLC and HPLC analysis of urines and faeces extracts revealed a complex metabolite pattern which was independent of the dose level and sex of the animals. However, some minor quantitative differences between the dose levels and the sexes were observed. Only one metabolite fraction, being present in the urine, exceeded 10% of the dose. All other urine and faeces metabolites were typically below 5% of the administered dose. In the faeces of animals dosed with 100 mg/kg body weight small amounts of unchanged dimethachlor were detected (< 1% of the dose). The biliary metabolite profile, as determined by HPLC, consisted of about 9 metabolite fractions. At the low dose level, the 3 major fractions accounted for 15%, 22%, and 25% of the administered dose. The corresponding fractions at the high dose level amounted to 6%, 14%, and 15% of the administered dose. E: The excretion route was independent of the dose level, but significantly different for both sexes. Within 7 days about 40% and more than 60% of the administered dose were renally excreted by male and female rats, respectively.		[redacted] & [redacted] (1994)

Method	Results	Remarks	Reference
	Totally 89% to 92% of the dose were excreted within this time period. At the low dose level bile-duct cannulated male rats excreted within 48 hours about 90%, 4%, and 2% of the dose with the bile, urine, and faeces, respectively. The excretion by bile, urine, and faeces at the high dose level within 42 hours was 68%, 22%, and 1% of the dose, respectively. Enterohepatic circulation was significantly involved in the disposition of dimethachlor.		
Radioactive *in vitro* binding assay using rat and human blood. Human: Venous blood from a healthy volunteer, heparinized. Rat Tif: RAIf (SPF): blood from the jugular vein, heparinized [U-^{14}C]phenyl 2-chloro-N-(2,6-dimethylphenyl)-N-(2-methoxyethyl)-acetamide (radioactive dimetachlor - CGA 17020) 4 µg radiolabelled test substance (1 µg/g blood; applied activity ca. 11.6 kBq) Vehicle: Phosphate buffered saline, pH 7.3 4 hr incubation at 37°C	In rat blood the radioactivity was mainly present in the protein fraction of the cytoplasm (62.6%) and in the ghosts fraction (33.5%) whereas the plasma, including the blood cell wash, contained only 3.9%. The activity found in the non-protein fraction of the cytoplasm and in the protein wash was below the limit of determination. There is strong evidence that the radioactivity detected in the ghosts fraction was due to test substance covalently bound to haemoglobin co-precipitating with the ghosts. In human blood 80.7% of the radioactivity was present in the plasma (including the blood cell wash). The remaining activity was distributed between ghosts (0.1%), protein fraction of the cytoplasm (11.7%) and the non-protein fraction of the cytoplasm (7.6%, including protein wash). The amount of test substance found in the cytoplasmic protein and ghosts fraction was 8.2 times lower in human blood than in rat blood. Furthermore, the test substance found in the cytoplasmic protein fraction from human was attributed to non-covalent binding. The results strongly suggest that the persistent binding of dimethachlor to rat blood cells observed *in vivo* is attributed to a covalent binding to rat haemoglobin and is a species-specific phenomenon which is irrelevant for humans.		Löffler (1997)
Absorption, distribution, degradation, and excretion after multiple administrations in the rat. OECD 417 (2010). Oral (gavage) Rat (male) RAI:Tif (SPF) 4 M per group/5 groups [U-^{14}C]phenyl 2-chloro-N-(2,6-dimethylphenyl)-N-(2-methoxyethyl)-acetamide	After administration of the multiple doses to male rats, levels of total radioactivity in blood increased rapidly and in an almost linear manner. Maximum mean concentrations of radioactivity were observed at 24 hours after the last administration, with a mean value of 9.2 ppm CGA17020 equivalents. Thereafter levels of radioactivity in blood declined and reached 3.6 ppm CGA17020 equiv. at 22 days after the last administration. Half-lives of depletion in blood were calculated from the depletion phase	Tissue distribution time course of CGA 17020 in the rat after multiple oral administrations was strongly affected by the chemical property of the CGA 17020 to covalently bind	[redacted] (2000)

Method	Results	Remarks	Reference
(radioactive dimetachlor - CGA 17020) 14 doses of 0,5 and 100 mg/kg bw Vehicle: PEG 200/ethanol/water (1:1:2, v/v). 1, 7, 14,20 or 35 days observation	starting at 24 hours after the last administration. Assuming first order kinetics and mono-phasic elimination for the depuration of radioactivity from the blood, the mean half-life was calculated to be 16 ± 4 days. At seven days after the last administration of the [Phenyl-U-^{14}C] CGA17020, ca. 48 and 46% of the total dose were excreted via urine and faeces. An excretion steady state was reached 3 days after the first administration. In total, 93.9% of the administered dose were recovered in the excreta and the cage wash within seven days after the last administration. More than 90% of the test substance and/or its metabolites were excreted within 2 days after the last administration. Radioactivity in the excised organs and tissues amounted to 0.3% of the total administered dose and another 1.2% were recovered in the carcasses of the rats. Most of the systemically absorbed radioactivity that was found within the rat's body at this sampling point was associated with the whole blood. This finding can be attributed to the property of CGA17020 to covalently bind to the haemoglobin molecule of the rat's red blood cells. Consequently, 2.3% of the total dose was recovered in the blood collected at this sampling point. Neither rates nor routes of excretion changed during the administration period. Pooled urine and faeces extracts from specimen collected at 0 - 24 hours and 312 - 336 hours after the first administration were analysed by two-dimensional TLC. Qualitative and quantitative analysis revealed a complex metabolite pattern. Differences in the metabolite pattern of either the urine or the faeces extract after single or multiple administrations were not observed. Radioactive residues were determined in selected tissues and organs during and after the administration phase. Highest mean tissue levels of radioactivity were observed at 24 hours after the last dose administration (336 hours after first administration) for all tissue and organs but spleen. Highest concentrations of radioactive residues were found in whole blood (7.3 ppm CGA17020 equiv.) and in the well-perfused organs like lungs, kidney, liver, heart and thyroids (0.4 - 1.0 ppm CGA17020 equiv.). Less perfused organs had the lowest residues at all sampling points. Residue levels of CGA17020 in fat, testes and muscle did	to the rat haemoglobin molecule. . Accumulation of radioactivity due to chemical or physico-chemical properties of the molecule, other than the binding to the rat haemoglobin molecule, was not observed.	

Method	Results	Remarks	Reference
	not exceed 0.06 ppm CGA17020 equiv. at the 336 hours sampling point. Using the three data points for each organ (two data points for spleen) and assuming first order kinetics and mono-phasic elimination for the depletion of radioactive residues from the tissues, half-lives were estimated. Half-lives were typically in the range of 11-19 days for most tissues, but somewhat shorter for the less perfused organs. Longest half-lives of the radioactive residues were estimated for bone (20 days) and spleen (27 days), organs involved in the lifecycle of red blood cells.		
The metabolism of [U-14C] Phenyl CGA 17020 in the rat OECD 417(1984) Oral (gavage) Rat Tif: RAIf (SPF) 5 M, 5F (ADME) 4 M, 4F (blood levels) 9M, 9 F (tissue levels) 6 M (excretion low dose) 4 M (excretion highdose) [U-^{14}C]phenyl 2-chloro-N-(2,6-dimethylphenyl)-N-(2-methoxyethyl)-acetamide (radioactive dimetachlor - CGA 17020) single doses of 0,5 and 100 mg/kg bw Vehicle: PEG 200/ethanol/water (1:1:2, v/v). 7 days observation, 30 days for blood level groups	A total of 21 metabolites were isolated and identified by spectroscopic means (^{1}H-NMR, IR- and mass-spectroscopy): - N-carbamoylmethyl-N-(2,6-dimethyl-phenyl)-2-hydroxy-acetamide - N-(2,6-dimethyl-phenyl)-N-(2-hydroxy-ethyl)-2-methylsulfanyl-acetamide - 2-chloro-N-(2, 6-dimethyl-phenyl)-N-(2-hydroxy-ethyl)-acetamide - 2-acetylamino-3-{[(2,6-dimethyl-phenyl)-(2-methoxy-ethyl)-carbamoyl] methylsulfanyl}-propionic acid - 6-{2-[chloroacetyl-(2,6-dimethyl-phenyl)-amino]-ethoxy}-3,4,5-trihydroxy tetrahydro-pyran-2-carboxy lie acid - 2-acetylamino-3-{[(2,6-dimethyl-phenyl)-(2-hydroxy-ethyl)-carbamoyl] methylsulfanyl}-propionic acid - [(2,6-dimethyl-phenyl)-hydroxyacetyl-amino]-acetic acid - 6-{2-[chloroacetyl-(2-methoxy-ethyl)-amino]-3-methyl-benzyloxy}-3, 4,5- trihydroxy-tetrahydro-pyran-2-carboxylic acid - N-(2,6-dimethyl-phenyl)-N-(2-hydroxy-ethyl)-2-methanesulfonyl-acetamide - 2-acetylamino-3-[(2,6-dimethyl-phenylcarbamoyl)-methylsulfanyl]-propionic acid - 6-{2-[(2,6-dimethyl-phenyl)-methanesulfonylacetyl-amino]-ethoxy}-3, 4,5- trihydroxy-tetrahydro-pyran-2-carboxylic acid	Continuation of the toxicokinetic study by [redacted] and [redacted], 1994.	[redacted] (1996)

Method	Results	Remarks	Reference
	- N-(2,6-dimethyl-phenyl)-2-methanesulfinyl-N-(2-methoxy-ethyl)-acetamide - 2-acetylamino-3-{[(2-hydroxy-ethyl)-(2-hydroxymethyl-6-methyl-phenyl) carbamoyl]-methylsulfanyl}-propionic acid - 6-{2-[chloroacetyl-(2-hydroxy-ethyl)-amino]-3-methyl-benzyloxy}-3, 4,5- trihydroxy-tetrahydro-pyran-2-carboxylic acid - N-(2-hydroxy-ethyl)-N-(2-hydroxymethyl-6-methyl-phenyl)-acetamide - N-(2,6-dimethyl-phenyl)-N-(2-hydroxy-ethyl)-2-methanesulfinyl-acetamide - 2-amino-3-{[(2,6-dimethyl-phenyl)-(2-methoxy-ethyl)-carbamoyl] methylsulfanyl}-propionic acid - 2-amino-4-(1-carboxy-2-{[(2,6-dimethyl-phenyl)-(2-methoxy-ethyl) carbamoyl]-methylsulfanyl}-ethylcarbamoyl)-butyric acid - [acetyl-(2,6-dimethyl-phenyl)-amino]-acetic acid - 6-{2-[(2,6-dimethyl-phenyl)-methanesulfinylacetyl-amino]-ethoxy}-3,4,5- trihydroxy-tetrahydro-pyran-2-carboxylic acid - 6-{2-[(2,6-dimethyl-phenyl)-methylsulfanylacetyl-amino]-ethoxy}-3,4,5- trihydroxy-tetrahydro-pyran-2-carboxylic acid In addition, oxalic acid derivatives were characterized. Based on the structures of these metabolites the following metabolic pathways for dimethachlor are proposed: - O-dealkylation leading to a primary alcohol, followed partially by oxidation to the ultimate carboxylic acid (major pathway) - substitution of the chlorine with glutathione, followed by degradation of the glutathione moiety resulting in various S-containing metabolites, i.e. cysteinates, mercapturates, sulfides, sulfoxides and sulfones (major pathway) - oxidation of the methyl-phenyl group resulting in a primary alcohol (major pathway)		

Method	Results	Remarks	Reference
	- substitution of the chlorine by an OH-group yielding the corresponding hydroxyl derivative, followed partially by oxidation to an oxalic acid derivative (minor pathway) - reduction of the CH_2Cl-moiety to a methyl group (minor pathway) - N-dealkylation giving rise to a secondary amide (minor pathway) Most of the metabolites were the result of more than one transformation. Hydroxylated metabolites were partially conjugated with glucuronic acid. Evidence for the absence of free aniline derivatives was generated by chemical derivatization procedures. The degradation resulted in metabolites which were eliminated mainly via the bile and ultimately via faeces or urine after reabsorption from the intestinal tract into the systemic circulation and after enterohepatic circulation and further transformation of the primary bile specific metabolites. Consequently, a moderate excretion rate and rather complex metabolite pattern in urine and faeces were observed. The extent of dimethachlor degradation was independent on dose and sex. Almost complete degradation took place. This reflected the high extent of absorption at both dose levels. Therefore, the major metabolic pathways postulated were not significantly influenced by the sex of the animals and the dose level within the limits of this study. The sex dependent difference in elimination routes was therefore not a result of unique metabolism in one sex but was related to a difference in relative abundance and preferred route of elimination of common metabolites.		
Absorption, Excretion and Kinetics of [14C] Dimethachlor Following Single Oral Administration in the Rat. OECD 417 (2010) Oral (gavage) Rat Tif: RAIf (SPF) 4 M, 5F (ADME) 4 M per group [U-^{14}C]phenyl 2-chloro-N-(2,6-dimethylphenyl)-N-(2-methoxyethyl)-acetamide	Irrespective of dose, following a single oral administration of [14C] dimethachlor, the majority of dose related radioactivity was eliminated by 48 hours post dose and excretion nearing completion by 168 h. Absorption was not limited by dose with >97% absorbed across both doses. The majority of the absorbed dose was excreted via biliary elimination. Overall, within the same dose levels total systemic exposure to whole blood was vastly greater than observed in plasma due to a maintained affinity with the cellular fraction. Systemic exposure was not limited by absorption, as reflected by		[redacted] & [redacted] (2018)

Method	Results	Remarks	Reference
(radioactive dimetachlor - CGA 17020) single doses of 0,5 and 100 mg/kg bw Vehicle: PEG 200/ethanol/water (1:1:2, v/v). 7 days observation, 3 days for duct cannulated groups	the supra-proportional increase in systemic exposure between the 0.5 mg/kg and 100 mg/kg doses. Dimethachlor was detected in faeces from bile duct cannulated rats only (<0.1% dose). Metabolites of dimethachlor were numerous and accurate quantification was difficult due to lack of chromatographic resolution and peak geometry. Metabolism of dimethachlor was extensive and the biotransformation followed two main routes. One pathway resulted in substitution of the chlorine *via* a glutathione pathway. The glutathione conjugate was not observed, however, cysteine conjugates (Metabolite 14), cysteinyl-glycine conjugates (Metabolites 3 and 12), mercapturates (Metabolites 2 and 9), a methyl sulphide (CGA48083), sulphoxides (CGA48085, CGA48088, Metabolites 5 and 7) and a sulphone (Metabolite 1) provided evidence of this metabolic route. The other pathway resulted from oxidation (Metabolites 6, 11 and 13) and glucuronidation (Metabolites 4, 8 and 10). It was not possible to determine whether oxidation occurred on the methyl moieties on the benzene ring or directly on the benzene ring. Both pathways functioned for dimethachlor and CGA39026 (*O*-demethylated dimethachlor). There was no evidence to indicate the presence of radiolabelled metabolites formed by substitution of the chlorine *via* a glutathione pathway that had also lost the alkyl side chain. There was no evidence for loss of the side chain to form the primary or secondary amines 2,6 dimethylaniline and N-(2,6-dimethylphenyl)chloroacetamide, which were analysed as reference standards.		
CGA017020 – in vitro comparative metabolism of [phenyl-u-14c]-cga017020, in human, rat, mouse, rabbit and dog liver microsomes . Pool of mixed gender human, Wistar rat, CD1 mouse, New-Zealand rabbit, and Beagle dog liver microsomes [phenyl-U-14C]-CGA017020	Positive control enzymatic activities (testosterone 6β-hydroxylation and 7-ethoxycoumarin O-dealkylation) showed that the liver microsomes possessed metabolic competences in agreement with the acceptance criteria. Negative controls indicated that CGA017020 did not degrade in the incubation medium. Metabolism of CGA017020 was observed in human and animal liver microsomes after 60 minutes of incubation. Remaining parent CGA017020 accounted for 43.7%, 4.7%, 2.5% and 11.4% of the dose in human,		Thibaut (2019.)

Method	Results	Remarks	Reference
10 µM with NADPH-incubation 60 minutes at 37°C.	rat, mouse and dog, respectively. CGA017020 was fully metabolised in rabbit. Up to 9 radio-HPLC peaks (P1 to P9) were observed in the microsome incubates. P9 corresponded to unchanged CGA017020. Metabolism of CGA017020 was NADPH-dependent in human and animal liver microsomes. In human, P5, P4, and P7 were the main metabolites observed, accounting for 27.3%, 13.5% and 6.9% of the dose respectively. P2, P3, P6, and P8 were minor metabolites (≤ 3.1%). The metabolic pattern of CGA017020 observed in rat, mouse, rabbit and dog was qualitatively similar to human. All the metabolites formed in human were detected in animal liver microsomes. In a validated in vitro test system, the metabolism of CGA017020 in liver microsomes was qualitatively similar between human, rat, mouse, rabbit and dog; with no unique human metabolites observed.		

2.6.1.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

After oral administration to rats, dimethachlor was almost completely absorbed from the intestinal tract as was evident from experiments with bile-cannulated rats. Within 7 days 88.7 to 96.6 % of the dose was excreted. A sex dependent, but dose independent excretion pattern was observed: the amount of radioactivity excreted with the urine and faeces was about equal in males, whereas females excreted about 2/3 of the dose with the urine and about 1/3 with the faeces. The bile is the primary excretion route with up to 90 % of the dose excreted via this route. Substantial amounts of biliary excreted radioactivity is re-absorbed from the intestine and finally excreted with the urine, indicating that enterohepatic circulation takes place. Based on urinary and biliary excretion and carcass residues the rate and extent of absorption exceeds 94 % in both sexes.

Residual radioactivity in organs and tissues after a single oral low dose was determined after 1, 7, 15 and 29 days in males and after 1, 7, 10, and 19 days in females. The highest residual radioactivity was determined in (whole) blood and highly perfused organs (lungs, heart, kidneys, liver, spleen). Half-life times ranged between 3 (plasma in males) and 49 days (lungs in females). While in whole blood and highly perfused organs a monophasic first order depletion kinetic was observed, a biphasic first order kinetic with shorter half-life times, especially for the first phase, were observed in plasma and less perfused organs. The tissue distribution time course of dimethachlor in the rat after multiple oral administrations was strongly affected by the chemical property of the dimethachlor to bind covalently to the rat haemoglobin molecule. After the end of the exposure phase, dimethachlor and/or its metabolites were eliminated from the organs and tissues with half-lives of typically 2 – 3 weeks. Accumulation of radioactivity due to chemical or physico-chemical properties of the molecule, other than the binding to the rat haemoglobin molecule, was not observed.

Comparison of the distribution of radioactivity after incubation of radiolabelled dimethachlor with rat and human blood revealed that the persistent binding of dimethachlor to rat blood is most likely attributed to a covalent binding to rat haemoglobin, whereas the covalent binding to human haemoglobin is unlikely. This difference in behaviour may be due to differences in the structure of human and rat haemoglobin. The β-chain of rat haemoglobin contains a reactive cysteine residue (Cys β-125) that is available for the reaction with the activated carbon atom in the chloracetyl moiety of dimethachlor and other chloracetanilids. In contrast to that, in human haemoglobin there is no

reactive cysteine residue. Therefore, there is strong evidence that the binding of dimethachlor to rat blood is a species-specific phenomenon that is not relevant to humans.

The metabolic pathway of dimethachlor was determined in rats. The degradation of dimethachlor led to a complex pattern of metabolites and was almost complete as indicated by the fact that only traces of parent compound (≤ 0.1 % of the administered dose) were detected in the excreta. The metabolism was independent of the administered dose and the sex of the animals. Minor quantitative differences in the amount of certain metabolites were probably due to the differences in the elimination route rather than the result of a sex specific metabolism.

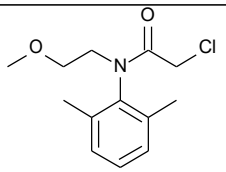
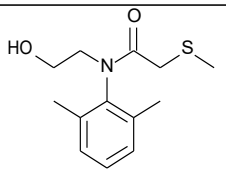
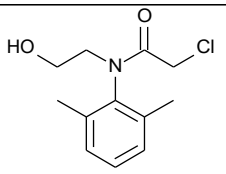
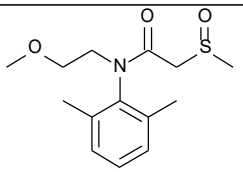
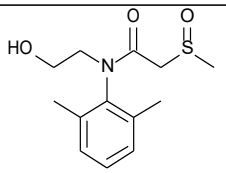
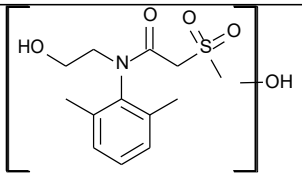
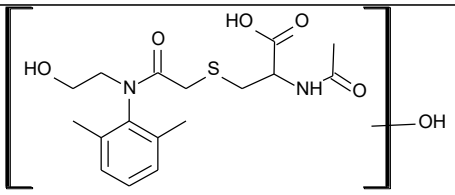
Metabolism of dimethachlor was extensive and the biotransformation followed two main routes. One pathway resulted in substitution of the chlorine via a glutathione pathway. The glutathione conjugate was not observed, however, cysteine conjugates, cysteinyl-glycine conjugates, mercapturates, a methyl sulphide, sulphoxides and a sulphone provided evidence of this metabolic route. The other pathway resulted from oxidation and glucuronidation following O-demethylation. Both pathways functioned for dimethachlor and CGA39026 (O-demethylated dimethachlor). Minor metabolic pathways were the reduction of the methylene chloride moiety (-CH_2Cl) giving rise to acetyl derivatives, the replacement of the chlorine by –OH and the subsequent oxidation to oxalic acid derivatives. There was no evidence to indicate the presence of radiolabelled metabolites formed by substitution of the chlorine via a glutathione pathway that had also lost the alkyl side chain. There was also no evidence for loss of the side chain to form the primary or secondary amines, 2,6 dimethylaniline and N-(2,6-dimethylphenyl) chloroacetamide, which were analysed as reference standards, or the sulphate ester of the p-hydroxylated aniline.

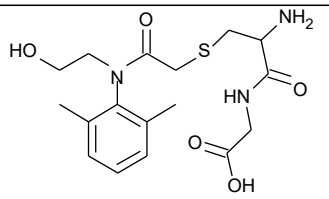
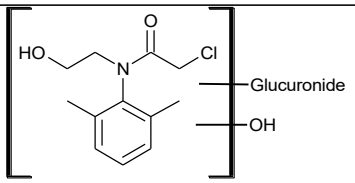
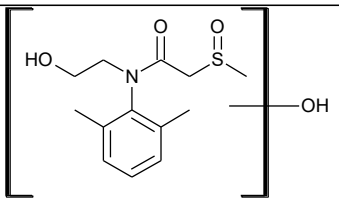
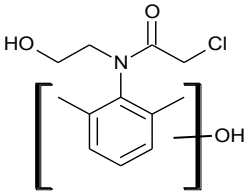
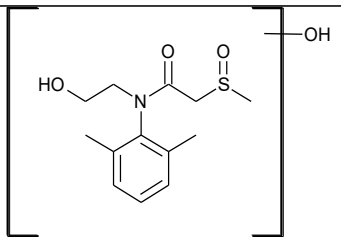
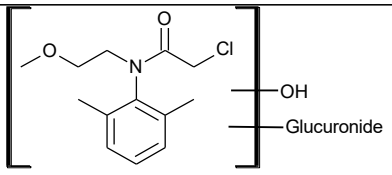
In vitro metabolic profiling of CGA017020 carried out in human, Wistar rat, CD1 mouse, New-Zealand rabbit, and Beagle dog by incubating liver microsomes with 10 µM of [phenyl-U-^{14}C]-CGA017020 and a NADPH-regenerating system for 60 minutes at 37°C, showed that the metabolism of CGA017020 in liver microsomes was qualitatively similar between human, rat, mouse, rabbit and dog; with no unique human metabolites observed.

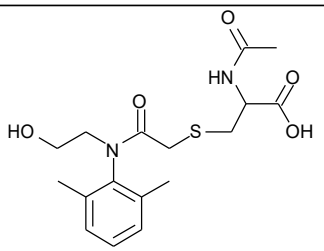
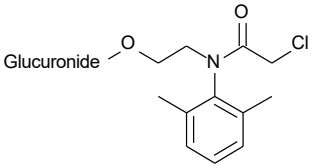
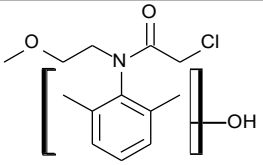
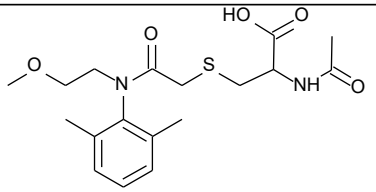
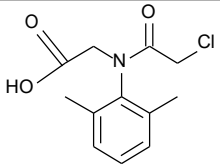
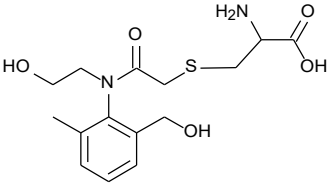
Summary of ADME endpoints

Rate and extent of oral absorption/systemic bioavailability	> 94 % (based on urinary and biliary excretion and tissue residues within 168 h)
Toxicokinetics	At 1 and 100 mg/kg, respectively Plasma C_{max}: 0.05 & 12 µg equiv/g, t_{max} 0.25 & 8h, $t_{1/2}$; 27-34 h. $AUC_{(0-t)}$ 1.39 & 380 µg equiv.h/mL.
Distribution	Initially widely distributed; highest residues in highly perfused organs (lungs, heart, kidneys, liver, spleen).
Potential for bioaccumulation	Accumulation due to the binding of dimethachlor to the rat haemoglobin molecule (rat specific).
Rate and extent of excretion	>91 % within 168 h, mainly via urine (44.14 % male; 59.79 % female) and via faeces (47.07 % male, 30.95 % female)

Metabolites of [^{14}C]-dimethachlor found in the rat

Metabolite Class	Structure
Dimethachlor	 $C_{13}H_{18}ClNO_2$ MW 255 Da
CGA48083	 $C_{13}H_{19}NO_2S$ MW 253 Da
CGA39026	 $C_{12}H_{16}ClNO_2$ MW 241 Da
CGA48085	 $C_{14}H_{21}NO_3S$ MW 283 Da
CGA48088	 $C_{13}H_{19}NO_3S$ MW 269 Da
Metabolite 1	 $C_{13}H_{19}NO5S$ MW 301 Da
Metabolite 2	 $C_{17}H_{24}N_2O_6S$ MW 384 Da

Metabolite Class	Structure
Metabolite 3	 $C_{17}H_{25}N_3O_5S$ MW 383 Da
Metabolite 4	 $C_{18}H_{24}ClNO_9$ MW 433 Da
Metabolite 5	 $C_{13}H_{19}NO_4S$ MW 285 Da
Metabolite 6	 $C_{12}H_{16}ClNO_3$ MW 257 Da
Metabolite 7	 $C_{13}H_{19}NO_4S$ MW 285 Da
Metabolite 8	 $C_{19}H_{26}ClNO_9$ MW 447 Da

Metabolite Class	Structure
Metabolite 9	 $C_{17}H_{24}N_2O_5S$ MW 368 Da
Metabolite 10	 $C_{18}H_{24}ClNO_8$ MW 417 Da
Metabolite 11	 $C_{13}H_{18}ClNO_3$ MW 271 Da
Metabolite 12	 $C_{18}H_{26}N_2O_5S$ MW 382 Da
Metabolite 13	 $C_{12}H_{14}ClNO_3$ MW 255 Da
Metabolite 14	 $C_{15}H_{22}N_2O_5S$ MW 342 Da

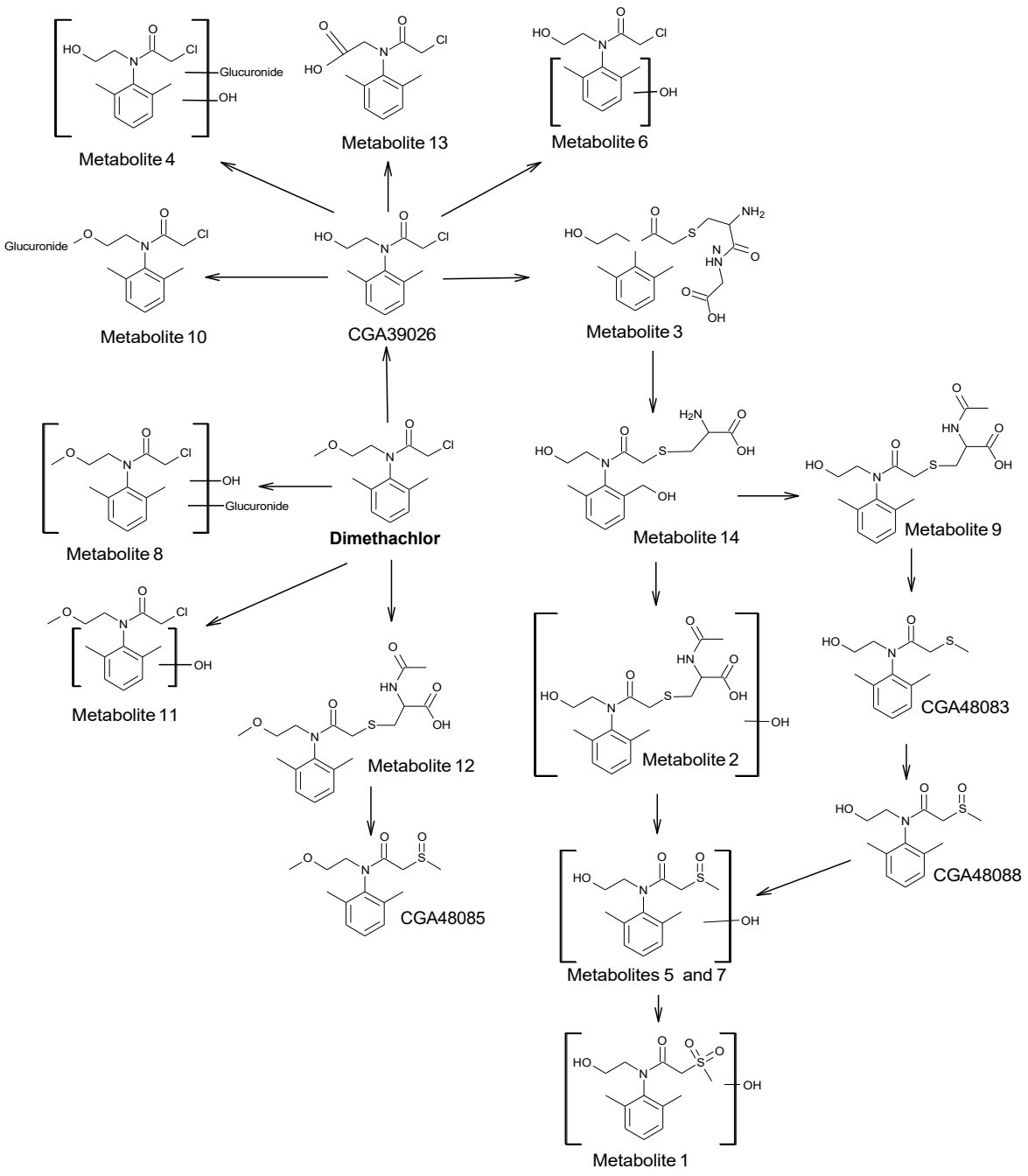


Figure 2.6.1-1: Biotransformation Pathway Based on Identified Metabolites of Dimethachlor

2.6.2 Summary of acute toxicity

2.6.2.1 Acute toxicity - oral route [equivalent to section 10.1 of the CLH report template]

Table 9: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Acute oral (gavage) OECD 401 (1987) GLP	Rat Tif:RAI f (SPF) 5 /sex - 2000 mg/kg bw 5 females – 1000 mg/kg bw	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: 0.5% CMC in 0.1% (w/v) aqueous polysorbate 80.	2000 mg/kg bw. 1000 mg/kg bw (females only). Single dose followed by 14 day observation period.	Estimated LD_{50}: **Males**: >2000 mg/kg bw. **Females**: >1000, approx. 2000 mg/kg bw. **Both sexes**: ≥2000 mg/kg bw.	[redacted] (1993a)
Acute oral (gavage) Non guideline study Conducted prior to GLP Limitations in design +/or reporting Supplementary only.	Rat Tif:RAI f (SPF) 5 /sex /group	Dimethachlor (CGA17020) technical. Batch: Not reported Purity: Not reported Vehicle: 2% CMC.	1000, 1290, 1670, 2150 or 3170 mg/kg bw. Single dose followed by 7 day observation period.	Calculated LD_{50}: **Both sexes**: 1600 (1250-2048) mg/kg bw.	[redacted] (1973)

Table 10: Summary table of human data on acute oral toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 11: Summary table of other studies relevant for acute oral toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

2.6.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

In an acute oral toxicity study ([redacted], 1993a), 5 male and 5 female rats were dosed (by gavage) at 2000 mg/kg bw and 5 females were dosed (by gavage) at 1000 mg/kg bw, followed by an observation period of 14 days. Clinical signs observed after dosing at 1000 or 2000 mg/kg bw included piloerection, hunched posture and dyspnoea. Reduced locomotor activity was also seen after dosing at 2000 mg/kg bw. At 2000 mg/kg bw, two females died spontaneously within 24 hours of dosing. Surviving animals recovered within 4 to 6 days. No abnormalities were seen at necropsy. The acute oral median lethal dose for dimethachlor was determined as: greater than 2000 mg/kg body weight for male rats; greater than 1000, approximately 2000 mg/kg body weight for female rats; equal to or greater than 2000 mg/kg body weight for both sexes.

In an older, pre-guideline and pre-GLP acute oral toxicity study in rats ([redacted] 1973), 5 male and 5 female rats per

group were dosed (by gavage) at 1000, 1290, 1670, 2150 or 3170 mg/kg bw, followed by an observation period of 7 days. Clinical signs were observed at all dose levels within 2 hours of dosing and included sedation, dyspnoea, exophthalmos, curved position, trismus, tonic-clonic muscle spasms and ruffled fur. Mortalities were seen in 1/2, 3/3, 2/5 and 5/5 males/females at doses of 1290, 1670, 2150 and 3170 mg/kg bw, respectively. There were no mortalities in males or females dosed at 1000 mg/kg bw. Surviving animals recovered within 4 to 7 days. No gross abnormalities were seen at examination post mortem. The acute oral LD50 dose for dimethachlor was calculated as 1600 (1250-2048) mg/kg body weight for both sexes (according to Lichfield and Wilcoxon, 1949). These results are considered as a supplementary evidence. Namely, although the study's methodology was generally in agreement with OECD TG 401 (1981, 1987), this is a non-GLP study with deficiencies in study reporting regarding the test material used (i.e. lack of information on purity, content and stability of active substance).

2.6.2.1.2 Comparison with the CLP criteria regarding acute oral toxicity

As the acute oral median lethal dose of dimethachlor in female rats was estimated to be less than the upper criterion of 2000 mg/kg bw, the data meet the criteria for classification and labelling. This classification is supported by the LD50 value of 1600 mg/kg bw determined in the earlier (pre-guideline and pre-GLP) study.

2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity

The appropriate classification for dimethachlor is Acute Tox Cat 4 H302: Harmful if swallowed.

2.6.2.2 Acute toxicity - dermal route [equivalent to section 10.2 of the CLH report template]

Table 12: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
Acute dermal toxicity OECD 402 (1987) GLP	Rat Tif:RAIf (SPF) 5/ sex / group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: 0.5% CMC in 0.1% (w/v) aqueous polysorbate 80.	2000 mg/kg bw. 24 hour application followed by a 14 day observation period.	>2000 mg/kg bw Males/females	[redacted] (1993b)

Table 13: Summary table of human data on acute dermal toxicity

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant data				

Table 14: Summary table of other studies relevant for acute dermal toxicity

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant studies				

2.6.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

In an acute dermal toxicity study ([redacted], 1993b), rats were exposed to the limit dose of 2000 mg/kg bw for 24 hours, followed by a 14 day observation period. Approximately 24 hours before treatment an area on the back of the rat (of at least 10% of the body surface) was shaved with an electric clipper. The test article was evenly dispersed

on the skin. It was covered with a gauze-lined semi-occlusive dressing fastened around the trunk with an adhesive elastic bandage. After 24 hours, the dressing was removed and the skin was cleaned with lukewarm water. Thereafter, the animals were examined daily and skin reactions were appraised repeatedly. There were no mortalities. Clinical signs were limited to the presence of piloerection on the day of application. No abnormalities were seen at necropsy.
The acute dermal median lethal dose for male and female rats was in excess of 2000 mg/kg body weight (limit test).

2.6.2.2.2 Comparison with the CLP criteria regarding acute dermal toxicity

As the acute dermal median lethal dose of dimethachlor is greater than the upper cut-off of 2000 mg/kg bw, the data do not meet the criteria for classification and labelling.

2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

No classification. No change to the existing decision on classification (i.e. no classification) is proposed.

2.6.2.3 Acute toxicity - inhalation route [equivalent to section 10.3 of the CLH report template]

Table 15: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value LC_{50}**	**Reference**
Acute inhalation (nose-only) OECD 403 (1981) GLP	Rat Tif:RAIf (SPF) 5/ sex / group Control group (5/sex) dosed alongside the test group.	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: ethanol Aerosol: generated from a 10% w/w solution of test item in ethanol MMAD: 1.2 – 2.2 µm	4.45 mg/ L air (limit test). 4 hour inhalation exposure followed by a 14 day observation period.	LC_{50}: Males & Females: >4.45 mg/L air.	[redacted] (1994)

Table 16: Summary table of human data on acute inhalation toxicity

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant data				

Table 17: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant studies				

2.6.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In an acute inhalation toxicity study ([redacted], 1994), 5 male and 5 female rats were exposed, nose-only, to a 10% w/w solution of dimethachlor in ethanol for 4 hours, at a mean gravimetric concentration of 4.45 mg/L, followed by a 14 day observation period. A control group was exposed to the vehicle (ethanol) under the same conditions as the test group. Two gravimetric measurements of particle size distribution during the exposure produced mass median aerodynamic diameters (MMAD) of 1.2 and 2.2 µm and geometric standard deviations (GSD) of 2.3 and 2.7, respectively. At least 94% of the aerosol was <7 µm. There were no mortalities during the study. Clinical signs after exposure included piloerection, hunched posture, dyspnoea and reduced locomotor activity, observed in both sexes

to a similar extent. All animals had recovered within 3 days. Body weights were unaffected by treatment and there were no treatment related macroscopic findings at necropsy.
The acute median lethal dose following nose-only inhalation exposure to dimethachlor, was greater than 4.45 mg/L in male and female rats. The mean concentration of 4.45 mg/L was the highest stable concentration attainable for this test material and was thus considered a limit dose.

2.6.2.3.2 Comparison with the CLP criteria regarding acute inhalation toxicity

As the acute inhalation median lethal concentration of dimethachlor aerosol is greater than the highest concentration that it was possible to generate, i.e. 4.45 mg/L, which is near to the classification threshold value of 5 mg/L, and since no mortality was observed up to 4.45 mg/L, it is considered that the data do not meet the criteria for classification and labelling.

2.6.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

No classification. No change to the existing decision on classification (i.e. no classification) is proposed.

2.6.2.4 Skin corrosion/irritation [equivalent to section 10.4 of the CLH report template]

Table 18: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Results** **- Observations and time point of onset[2]** **- Mean scores/animal** **- Reversibility**	**Reference**
Acute dermal irritation OECD 404 GLP	Rabbit New Zealand white (Chbb:NZW) 3 females	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w	0.5 g applied to shorn flank, moistened with water. Control patch (blank). 4 hour topical semi-occlusive application to intact skin. Irritation response assessed at 1, 24, 48 & 72 hours and at 7 days after removal of dressings.	Very slight to well defined erythema (score 1-2) and very slight to slight oedema (score 1-2) was present in 2/3 animals from 1 – 72 hours. In the 3rd animal, well defined to moderate to severe erythema (score 2-3) and slight to moderate oedema (scores 2-3) were present from 1-48 hours. Very slight erythema, very slight oedema (score 1) and scaling of the skin were present at 72 hours. Mean scores at 24, 48 and 72 hours: Erythema: 1.67, 1.33, 2.33 Oedema: 1.33, 1.33, 2.0 No signs of skin irritation (erythema or oedema) were present at 7 days (3/3 animals). Reversibility – 7 days.	[redacted] (1993a)

Table 19: Summary table of human data on skin corrosion/irritation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant data				

Table 20: Summary table of other studies relevant for skin corrosion/irritation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

2.6.2.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

The skin irritation / corrosion potential of dimethachlor was assessed in female New Zealand White rabbits ([redacted], 1993a). 0.5 g of dimethachlor was applied to the shaved flank for 4 hours under a semi-occlusive dressing. Skin reactions were evaluated at 1, 24, 48 and 72 hours after removal of the gauze patches. In order to determine the reversibility of the skin reactions, additional evaluation of the treated skin was necessary after 7 days. Individual mean scores for erythema (at 24, 48 and 72 hours) were 1.67, 1.33 and 2.33. Individual mean scores for oedema (at 24, 48 and 72 hours) were 1.33, 1.33 and 2.00 for the 3 rabbits. There were no signs of skin irritation at 7 days.
Also, no irritation was observed following epidermal applications of 30% and 50% dimethachlor in vaseline in the pre-tests for skin sensitisation study (CGA 17020 tech. - Skin Sensitisation Test in the Guinea Pig Maximisation Test, [redacted], 1993b).

2.6.2.4.2 Comparison with the CLP criteria regarding skin corrosion/irritation

Mean scores for erythema formation or oedema of ≥2.3 were present in 1/3 rabbits at 24, 48 and 72 hours. For 2/3 rabbits, the mean scores for erythema and oedema at 24, 48 and 72 hours were below the threshold for classification (≥2.3). The data therefore do not meet the criteria for classification (mean scores of ≥2.3 present in at least 2 out of 3 animals).

2.6.2.4.3 Conclusion on classification and labelling for skin corrosion/irritation

No classification. No change to the existing decision on classification (i.e. no classification) is proposed.

2.6.2.5 Serious eye damage/eye irritation [equivalent to section 10.5 of the CLH report template]

Table 21: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results - Observations and time point of onset[2] - Mean scores/animal - Reversibility	Reference
Acute eye irritation OECD 405 (1987) GLP	Rabbit New Zealand white (Chbb:NZW) 3 females	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w	0.1 mL (0.66 mg) Single exposure Control – untreated right eye. Irritation response assessed at 1, 24, 48 & 72 hours and at 7 days after instillation.	Conjunctival redness (scores 1-2) was present in 3/3 animals from 1-48 hours. Chemosis (score 1) was present in 3/3 rabbits from 1 - 24 hours. Iridial changes (score 1) were present in 3/3 rabbits at 1 hour and in 1/3 rabbits at 24 hours. Corneal opacity (score 1) was present in 1/3 rabbits at 24, 48 and 72 hours. **Mean scores/animal** (24, 48 and 72 hours): Conjunctivae (redness): 0.67, 1.0, 1.0 Conjunctivae (chemosis): 0.0, 0.33, 0.33	[redacted] (1993b)

<table>
<tr>
<td></td><td></td><td></td><td></td>
<td>Cornea: 0.0, 0.0, 1.0
Iris: 0.0, 0.33, 0.0

The mean scores (24-72 h) for individual animals are shown below:
<table>
<tr><th>Animal No</th><th>400</th><th>554</th><th>464</th></tr>
<tr><td>Conjunctiva – redness</td><td>0.67</td><td>1</td><td>1</td></tr>
<tr><td>Conjunctiva – chemosis</td><td>0</td><td>0.33</td><td>0.33</td></tr>
<tr><td>Cornea</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Iris</td><td>0</td><td>0.33</td><td>0</td></tr>
</table>
No signs of eye irritation were present at 7 days (3/3 animals).
Reversibility – 7 days.</td>
<td></td>
</tr>
</table>

Table 22: Summary table of human data on serious eye damage/eye irritation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 23: Summary table of other studies relevant for serious eye damage/eye irritation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

2.6.2.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

The eye irritation / corrosion potential of dimethachlor was assessed in female New Zealand White rabbits ([redacted], 1993b). 0.1 mL (0.66mg) of dimethachlor was applied to the conjunctival sac of the left eye. Ocular reactions were evaluated at 1, 24, 48 and 72 hours after instillation. In order to determine the reversibility of the eye reactions, additional evaluation of the eye was necessary after 7 days. Individual mean scores for corneal, iridial and conjunctival changes (at 24, 48 and 72 hours) were 1.0 or less. There were no signs of eye irritation at 7 days.

2.6.2.5.2 Comparison with the CLP criteria regarding serious eye damage/eye irritation

The mean values of the readings at 24 to 72 hours after instillation were below the threshold for classification. Namely, the CLP criteria for Category 2 eye damage/eye irritation require that a substance produces in at least in **2 of 3 tested animals** a positive response of **corneal opacity ≥ 1** and/or **iritis ≥ 1**, and/or **conjunctival redness ≥ 2** and/or **conjunctival oedema (chemosis) ≥ 2**, calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days.

At 24-72 h reading (according to the OECD scoring system), the mean score of 1 for corneal opacity was found in only one out of three tested animals; the mean score of 0.33 for iris was observed also in one animal, and the mean scores for conjunctival redness and chemosis were ≤ 1 in all three tested animals. All changes were fully reversible (score 0) after 7 days of observation. Therefore, it was concluded that dimethachlor does not fulfil the criteria for eye damage/eye irritation classification.

2.6.2.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

No classification. No change to the existing decision on classification (i.e. no classification) is proposed.

2.6.2.6. Respiratory sensitisation [equivalent to section 10.6 of the CLH report template]

Table 24: Summary table of animal studies on respiratory sensitisation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
No relevant studies					

Table 25: Summary table of human data on respiratory sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 26: Summary table of other studies relevant for respiratory sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

2.6.2.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No formally recognised and validated animal tests currently exist for respiratory sensitisation. Dimethachlor is a skin sensitiser based on guinea pig tests. There is no evidence of adverse effects from medical surveillance of manufacturing plant personnel. No cases of poisoning have been reported to the company. No epidemiological study has been performed by the company. No reports from the open medical literature are on record.

2.6.2.6.2 Comparison with the CLP criteria regarding respiratory sensitisation

As there are no specific animal data and no evidence in humans that dimethachlor exposure can lead to specific respiratory hypersensitivity, classification is not possible.

2.6.2.6.3 Conclusion on classification and labelling for respiratory sensitisation

No classification. No change to the existing decision on classification (i.e. no classification) is proposed.

2.6.2.7 Skin sensitisation [equivalent to section 10.7 of the CLH report template]

Table 27: Summary table of animal studies on skin sensitisation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
Maximisation test OECD 406 (1992) GLP	Guinea Pig Tif:DHP 1/sex - primary irritation test	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w	Intradermal induction (W1): Freund's adjuvant/saline mixture 1:1 (v/v). 5 % (w/v)	The concentrations were selected on the basis of pre-tests in separate animals. **Extreme skin sensitising potential** (according to maximisation grading of Magnusson and Kligman). All test animals (20/20) showed	[redacted] (1993c)

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
	10/sex – test group 5/sex – control group (induction with vehicle & adjuvant only)		CGA17020 in oleum arachidis; 5 % CGA17020 in Freund's adjuvant/saline mixture (w/v) Epidermal induction: (W2) 50 % (w/w) CGA17020 in Vaseline Epidermal challenge (W5): 50% CGA17020 w/v in Vaseline. Skin reactions were evaluated 24 and 48 hours after removal of dressings.	positive skin reactions 24 and 48 h after challenge. There were no positive skin reactions in the control animals or at the control sites of the test animals.	

Table 28: Summary table of human data on skin sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 29: Summary table of other studies relevant for skin sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

2.6.2.7.1 Short summary and overall relevance of the provided information on skin sensitisation

In a Maximisation skin sensitisation study in guinea pigs ([redacted], 1993c), a 5% preparation in Oleum arachidis was used for intradermal induction, and a 50% preparation in Vaseline (the highest concentration that could be technically prepared) was used for epidermal induction and for the challenge. These concentrations were determined based on the pre-test. Since epidermal application was not irritative, the application site was pretreated with 10% sodium lauryl sulfate 24 hours prior to the epidermal induction application.
Positive skin reactions were seen in 20/20 of the test animals at 24 and 48 hours after removal of the challenge dressings, corresponding to a sensitisation rate of 100%. There were no skin reactions among the control animals or on the control flanks of the test animals. Dimethachlor showed extreme skin sensitising (contact allergenic) potential in guinea pigs, according to the maximisation grading of Magnusson and Kligman.
The sensitivity of the test system was confirmed approximately 3 months before the conduct of the study using 2-mercaptobenzothiazole as the positive control. In this reliability study, 18/20 and 19/20 animals displayed signs of allergic skin reactions at the 24- and 48-hour readings, respectively.

2.6.2.7.2 Comparison with the CLP criteria regarding skin sensitisation

The test gave a positive result with 100% of the animals sensitised after an intradermal induction dose of 5%, which supports classification in subcategory 1B, according to the 2nd ATP criteria (Commission Regulation (EU) No 286/2011) (Table 27). However, subcategory 1A cannot be excluded due to the absence of an experiment with an intradermal induction dose of ≤ 1%. Therefore, skin sens. Category 1, without subcategorisation, is proposed.

2.6.2.7.3 Conclusion on classification and labelling for skin sensitisation

Dimethachlor should be classified as skin sensitizing Category 1 H317: May cause an allergic skin reaction. No change to the existing decision on classification (Skin Sens. 1 H317) is proposed.

2.6.2.8 Phototoxicity

Table 30: Summary table of studies on phototoxicity

Method, guideline, deviations[1] if any	Test substance	Dose levels duration of exposure	Results	Reference
Study not required				

A phototoxicity study is not required because dimethachlor does not absorb electromagnetic radiation in the range 290-700 nm.
The trigger for a phototoxicity study is a molar extinction coefficient, ε > 10 L/mol.cm at or above 290 nm. The molar extinction coefficient for dimethachlor is 3 L/mol.cm at 290 nm and drops away to the baseline at higher wavelength. Therefore, a phototoxicity study is not triggered.

Table 31: Summary table of human data on phototoxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 32: Summary table of other studies relevant for phototoxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

2.6.2.9 Aspiration hazard [equivalent to section 10.13 of the CLH report template]

Table 33: Summary table of evidence for aspiration hazard

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Not relevant				

2.6.2.9.1 Short summary and overall relevance of the provided information on aspiration hazard

Dimethachlor is a solid and no data have been generated to address aspiration hazard.

2.6.2.9.2 Comparison with the CLP criteria regarding aspiration hazard

As dimethachlor is a solid there is no risk of aspiration hazard.

2.6.2.9.3 Conclusion on classification and labelling for aspiration hazard

No classification. No change to the existing decision on classification (i.e. no classification) is proposed.

2.6.2.10 Specific target organ toxicity-single exposure (STOT SE) [equivalent to section 10.11 of the CLH report template]

Table 34: Summary table of animal studies on STOT SE (specific target organ toxicity-single exposure)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
OECD 401 Acute oral study GLP Rat (Tif: RAI f (SPF)) 5/sex/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 2000 mg/kg bw males and 2000 and 1000 mg/kg bw females Single oral dose followed by 14 days observation. Vehicle: 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80	**2000 mg/kg bw** *Mortality:*0/5 males and 2/5 females (died on day 1) *Clinical findings:* piloerection, hunched posture, dyspnea and decreased locomotor activity. *Macroscopic examination:* No abnormalities **1000 mg/kg bw** *Mortality:* 0/5 females *Clinical findings:* piloerection, hunched posture and dyspnea. *Macroscopic examination:* No abnormalities	[redacted] (1993a)
Acute oral study Rat (Tif: RAI) 5/sex/group	Dimethachlor (CGA17020) technical Batch: Not reported Purity: Not reported 3170, 2150, 1670, 1290 and 1000 mg/kg bw Single oral dose followed by 7 days observation. Vehicle: 2% (w/v) carboxymethylcellulose	**3170 mg/kg bw** *Mortality:*5/5 males and 5/5 females (all within 24 h) *Clinical findings:* sedation, dyspnoea, exophthalmos, curved position, trismus, tonic-clonic muscle spasms and ruffled fur. *Macroscopic examination:* No abnormalities **2150 mg/kg bw** *Mortality:*2/5 males and 5/5 females (all within 24 h) *Clinical findings:* sedation, dyspnoea, exophthalmos, curved position, trismus, tonic-clonic muscle spasms and ruffled fur. *Macroscopic examination:* No abnormalities **1670 mg/kg bw** *Mortality:*3/5 males and 3/5 females (5 within 24 h, 1 after 48 h) *Clinical findings:* sedation, dyspnoea, exophthalmos, curved position, trismus, tonic-clonic muscle spasms and ruffled fur. *Macroscopic examination:* No abnormalities **1290 mg/kg bw** *Mortality:*1/5 males and 2/5 females (all within 24 h)	[redacted] (1973)

		Clinical findings: sedation, dyspnoea, exophthalmos, curved position, trismus, tonic-clonic muscle spasms and ruffled fur. *Macroscopic examination:* No abnormalities **1000 mg/kg bw** *Mortality:*0/5 males and 0/5 females. *Clinical findings:* sedation, dyspnoea, exophthalmos, curved position, trismus, tonic-clonic muscle spasms and ruffled fur. *Macroscopic examination:* No abnormalities	
OECD 474 Micronucleus study GLP Mouse (NMRI) 5/sex/group	Dimethachlor (CGA17020) technical Batch: 1710 Purity 98.3% w/w Preliminary toxicity: 1000, 800, 600 mg/kg bw Single oral dose followed by 72 h observation. Main test: 600, 180, 60 mg/kg bw Single oral dose followed by 24 - 72 h observation. Vehicle: polyethylene glycol 400 (PEG 400)	**Preliminary toxicity** **1000 mg/kg bw** *Mortality:*2/2 males and 0/2 females. 1 male died 1 h after dosing and 1 male 48 h after dosing. *Clinical findings:* Decreased spontaneous activity, eyelid closure, apathy and abdominal position. **800 mg/kg bw** *Mortality:*2/2 males and 0/2 females. 1 male died 1 h after dosing and 1 male 24 h after dosing. *Clinical findings:* Decreased spontaneous activity, eyelid closure, apathy, abdominal position and convulsions. **600 mg/kg bw** *Mortality:*0/2 males and 0/2 females. *Clinical findings:* Decreased spontaneous activity, eyelid closure, apathy and abdominal position. **Main test** **600 mg/kg bw** *Mortality:*2/18 males and 0/18 females. No other information on clinical findings. **180 mg/kg bw** *Mortality:*0/6 males and 0/6 females. **60 mg/kg bw** *Mortality:*0/6 males and 0/6 females.	[redacted] (1991)
OECD 407 28 day repeat dose study GLP Rat (Tif: RAI f (SPF)) 10/sex/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 750/350, 150 and 30 mg/kg bw /day 28 days oral dose. Vehicle: 0.5% (w/v) carboxymethylcellulose in 0.1%	**750 mg/kg bw/day** *Mortality:*3/10 males and 2/10 females. (2 males and 1 female died on day 2, 1 female was sacrificed in moribund conditions, 1 male died on day 5) *Clinical findings:* creeping movement, hunched posture, hypoactivity and piloerection. Ataxia, convulsions, tremor, salivation and hypertension were observed in one female. All observations started on day 2 *Macroscopic examination:* Animals that were found dead or sacrificed: 2/10 males abnormal colour of the liver and mottled thymus. One of these males also showed abnormal colour of the kidney. Fluid contents in the thoracic cavity was observed in another male. Lungs of	[redacted] (1993)

	(w/v) aqueous polysorbate 80	the female that was sacrificed early were mottled. *Microscopic examination:* Animals that were found dead or sacrificed: Liver of 2 males and 2 females showed minimal to moderate and multifocal necrosis of hepatocytes. One male showed hepatocellular hypertrophy in the periportal region of the liver, 1 male showed hepatocellular hypertrophy diffusely distributed throughout the liver parenchyma. 3 males presented with minimal to moderate reduction of spermatogenesis. The thymus of 2 males showed minimal increase in the number of phagocytic cells (tangible body macrophages), expressing an increased lymphophagocytosis. Minimal to moderate dilation of the heart ventricles was observed in 2 males and 1 female. Due to mortality and marked signs of toxicity the highest dose was reduced from 750 to 350 mg/kg bw/day from experimental day 5. No observations were reported at 150 or 30 mg/kg bw /day after a single dose. No other observations relevant to this section as they occurred after multiple doses.	

Table 35: Summary table of human data on STOT SE (specific target organ toxicity-single exposure)

Type of data/report	**Test substance**	**Route of exposure Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant data				

Table 36: Summary table of other studies relevant for STOT SE (specific target organ toxicity-single exposure)

Type of study/data	**Test substance**	**Observations**	**Reference**
Developmental toxicity OECD 414 1981; short dosing period cf. OECD 414, 2018 GLP Rabbit, NZW strain 20 inseminated females/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 10, 100, 350, 600 mg/kg bw/day by oral gavage on gestation days 6-18 Vehicle 1.5% MC	***Maternal toxicity*** **<u>600 mg/kg bw/day</u>:** 3/3 deaths: 1/3 dead after one dose, 1/3 after two doses, 1/3 killed after two doses. No further animals allocated to group. **<u>350 mg/kg bw/day</u>:** 2/20 dead gestation days 18-20, 1/20 aborted day 22; ↓ body weight loss days 6-9 (-47%); ↓ body weight gain (35% days 6-19); ↓ food consumption (32% days 6-9, 18% days 9-12). **<u>100 mg/kg bw/day:</u>** No effects. ***Developmental toxicity*** **<u>350 mg/kg bw/day:</u>** No treatment-related effects. [↑ pre-implantation loss (43% cf. 23.5% controls) incidental to treatment but resulting in ↓ number live foetuses (5.5 cf. 8.4 controls) and	[redacted] (1993)

		↓ litter weight (35%) due to fewer foetuses. Also, high incidence of malformation in all groups including control; no effect of treatment indicated.] **NOAEL**: Maternal: 100 mg/kg/day Foetal: 350 mg/kg/day **LOAEL**: Maternal: 350 mg/kg/day Foetal: not determined	

2.6.2.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure (STOT SE)

In standard single dose dermal and inhalation toxicity studies there was no evidence of specific target organ toxicity. In these studies, there were non specific and no adverse effects observed. RMS noted that dyspnoea was one of the symptoms of inhalation exposure at or slightly below the limit dose for STOT-SE Cat 2 classification, however not specific for respiratory irritation as it is also noted after acute oral exposure. No human data are available that would indicate that Cat 3 H336 is warranted.

In a single dose oral toxicity study ([redacted], 1993a) mortality occurred after a single dose of 2000 mg/kg bw in females. There was no evidence of specific target organ toxicity. In this study, clinical signs were either non-specific or at dose levels resulting in lethality. In a pre-guideline and pre-GLP acute oral toxicity stu[redacted], 1973) mortality occurred after a single dose of 1290 mg/kg bw. Clinical observations of sedation, dyspnoea, exophthalmos, curved position, trismus, tonic-clonic muscle spasms and ruffled fur were reported at all dose levels, severity increased with increasing dose. The reported LD_{50} in this study was 1600 mg/kg. There was no evidence of specific target organ toxicity. In this study, any clinical signs were either non-specific or at dose levels resulting in lethality.

In a standard micronucleus study in the mouse mortality occurred after a single dose of 600 mg/kg bw ([redacted], 1991). There was no evidence of specific target organ toxicity. In this study, clinical signs were either non-specific or at dose levels resulting in lethality.

In a standard 28 day rat oral gavage study at 750 mg/kg bw/day (top dose tested) clinical observations of creeping movement, hunched posture, hypoactivity piloerection, ataxia, convulsions, tremor, salivation and hypertension were reported on day 2 ([redacted], 1993). On day 2 two males and one female were found dead and one female was sacrificed in moribund conditions. It is not evident in the report if these events occurred prior to, or after the second dose. On examination there were macroscopic and/or microscopic findings in the liver, kidney, testis, thymus, spleen, lung and heart. No mortality or treatment-related clinical signs were observed when this dose level was reduced to 350 mg/kg bw/day. No observations were reported at 150 or 30 mg/kg bw /day after a single dose. In this study, any adverse effects were either not specific to a target organ after single exposure, occurred after repeated dosing or at dose levels resulting in lethality. Additionally, dose level at which severe systemic toxicity was observed (750 mg/kg bw/day) is within dose range of $300 < ATE \leq 2000$ mg/kg bw corresponding to Category 4 for acute oral toxicity proposed for dimethachlor.

In the rabbit developmental study [redacted]1993), at 600 mg/kg bw/day one doe died after the first dose, one died after two doses, and one was killed after two doses. Accorind to CLP Regulation, "specific target organ toxicity (single exposure) is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance or mixture". Also, this dose level is within dose range of $300 < ATE \leq 2000$ mg/kg bw corresponding to Category 4 for acute oral toxicity proposed for dimethachlor. It is considered, therefore, that STOT SE classification is not justified based on these observations.

In all other repeated dose studies there were no relevant effects occurring after single exposures that were considered as evidence of specific target organ toxicity.

2.6.2.10.2 Comparison with the CLP criteria regarding STOT SE (specific target organ toxicity-single exposure)

Specific target organ toxicity (single exposure) is defined as specific, non-lethal target organ toxicity arising from a single exposure to a substance. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed effects are considered.

All adverse effects observed following a single dose of dimethachlor were not organ specific and/or were associated with mortality, consequently the data do not warrant classification.

Since transient sedation at a non-lethal dose level (1000 mg/kg bw) was observed in male and female rats in ([redacted] acute oral toxicity study, STOT-SE Category 3 classification for narcotic effects should be discussed. The CLP criteria for classifying substances as Category 3 for narcotic effects observed in animal studies "may include lethargy, lack of coordination, loss of righting reflex, and ataxia", and they should be transient in nature.
In this study, within 2 hours after dimethachlor treatment, the rats in all dosage groups showed sedation, dyspnoea, exophthalmus, curved position, trismus, tonic-clonic muscle spasms and ruffled fur. The surviving animals recovered within 4 to 7 days, and no gross abnormalities were seen at examination post mortem.
The RMS, however, considers that sedation in this study was accompanied by more severe symptoms indicating general toxicity rather than narcotic effects relevant for STOT-SE Cat. 3 classification. It should be also pointed out that this is a pre-GLP, pre-guideline study, with limited reporting. No individual data on clinical symptoms are available to the RMS and there are deficiencies in study reporting regarding the test material used (i.e. lack of information on purity, content and stability of active substance). The study is, therefore, considered as a supplementary evidence only.
On the other hand, in a GLP and OECD guideline compliant acute oral toxicity study by [redacted] (1993a), sedation was not observed, even at the lethal dose (2000 mg/kg bw) in rats. At a lower, non-lethal dose (1000 mg/kg bw), clinical findings included piloerection, hunched posture and dyspnea. There were no abnormalities on macroscopic examination.
Decreased spontaneous activity, eyelid closure, apathy and abdominal position were observed in [redacted] (1991) study in mice at a single oral dose that was not lethal in the pre-test. The animals recovered at 48 –hour observation time point after the treatment. Nevertheless, this dose level induced lethality in the main test (2/18 males died at that dose level).
The RMS, therefore, considers that although transient sedation, apathy and decreased spontaneous activity were observed in rats and mice after single oral administration of dimethachlor, they were accompanied with the signs of general toxicity (dyspnoea, exophthalmus, curved position, trismus, tonic-clonic muscle spasms, eyelid closure, abdominal position) and lethality. The RMS, therefore, considers that the evidence is not strong enough to justify classification for STOT-SE 3 for narcotic effects.

It can be concluded that a single dose with dimethachlor produced no effects that were considered to be indicative of organ dysfunction of relevance to human health. Classification for STOT-SE (Category 1, 2 or 3) is, therefore, not warranted.

2.6.2.10.3 Conclusion on classification and labelling for STOT SE (specific target organ toxicity-single exposure)

No classification. No change to the existing decision on classification (i.e. no classification) is proposed.

2.6.3 Summary of repeated dose toxicity (short-term and long-term toxicity) [section 10.12 of the CLH report]

2.6.3.1 Specific target organ toxicity-repeated exposure (STOT RE) [equivalent to section 10.12 of the CLH report template]

Table 37: Summary table of animal studies on repeated dose toxicity (short-term and long-term toxicity) STOT RE (specific target organ toxicity - repeated exposure)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
28 day repeated dose dietary toxicity study OECD 407 (1981) GLP: Yes Mouse: HanIBM:NMRI (SPF)	Dimethachlor (CGA17020) technical Batch: 1715 (identical with OP 110001) Purity: 96.8% w/w 0, 100, 1000,	**<u>7000 ppm (1493.3 mg/kg bw/day in males and 1783.7 mg/kg bw/day in females)</u>** *Body weight gain*: ↓ 37.0% males weeks 1-4. *Blood biochemistry*: ↑ 161.2% alanine amino-transferase activity females; ↑ 21.7% α2-globulin females. *Organ weights*: ↑ 37.8%, 34.6% liver to	[redacted] (1992b)

10/sex/group	3000, and 7000 ppm 0, 20.9, 204.4, 623.7, and 1493.3 mg/kg bw/day in males; 0, 23.2, 232.3, 715.2 and 1783.7 mg/kg bw/day	body weight ratios in males and females respectively; ↑ 20.2% kidney to body weight ratios in males. *Histopathology*: 10/10 hepatocyte hypertrophy both sexes (0/10 controls). **3000 ppm (623.7 mg/kg bw/day in males and 715.2 mg/kg bw/day in females)** *Organ weights*: ↑ 20.9%, 14.2% liver to body weight ratios in males and females respectively; ↑ 19.6% kidney to body weight ratios in males. *Histopathology:* 8/10 males 10/10 females hepatocyte hypertrophy (0/10 controls). **1000 ppm (204.4 mg/kg bw/day in males and 232.3 mg/kg bw/day in females)** *Organ weights*: ↑ 13.3% liver to body weight ratios in males; ↑ 17.3% kidney to body weight ratios in males. **100 ppm (20.9 mg/kg bw/day in males and 23.2 mg/kg bw/day in females)** No effects. **NOEL:** 100 ppm (20.9 mg/kg bw/day in males and 23.2 mg/kg bw/day in females). **LOEL**: 1000 ppm (204.4 mg/kg bw/day in males and 232.3 mg/kg bw/day in females **NOAEL**: 1000 ppm (204.4 mg/kg bw/day in males and 232.3 mg/kg bw/day in females) **LOAEL**: 3000 ppm (624 mg/kg bw/day in males and 715 mg/kg bw/day in females) - target organ: liver (increased absolute and relative liver weight, increased incidence of hepatocellular degeneration)	
25/26 day repeated dose dietary toxicity study OECD 407 (1981) GLP: Yes Rat: anIBM:WIST (SPF) 10/sex/group	Dimethachlor (CGA17020) technical Batch: 1715 (identical with OP 110001) Purity: 96.8% w/w 0, 100, 700, 3000, and 5000 ppm 0, 9.5, 67, 294.8 and 487.9 mg/kg bw/day in males; 0, 10.0, 68.3, 304 and 485.2 mg/kg bw/day in females	**5000 ppm (487.9 mg/kg bw/day in males and 485.2 mg/kg bw/day in females)** *Body weight gain*: ↓ 16.7% males, 10.9% females. *Food consumption*: ↓ 10.5% males, 7.5% females. *Haematology*: ↓ MCHC 2% males, 4% females (within historical control (HC) range); ↑ reticulocytes 13% females (non-significant, within HC range); ↑ proportion of immature reticulocyte fractions (3 times HFR, 1.3 times MFR). *Blood biochemistry*: ↑ total cholesterol 49.7% males 30.9% females; ↑ triglycerides 28.6% males 23.4 %females; ↑ Na 2.5% females; ↓ albumin 3.0% males 7.0% females; ↑ alpha-1 globulin 9.9% males 8.5% females. *Organ weights*: ↑ 23.1%, 16.3% liver to body weight ratios in males and females respectively. *Histopathology*: 10/10 hepatocyte hypertrophy both sexes (0/10 controls). **3000 ppm (294.8 mg/kg bw/day in males and 304.0 mg/kg bw/day in females)** *Body weight gain*: ↓ 7.5% males, 9.1%	[redacted] (1992a)

		females. *Food consumption*: ↓ 4.3% females. *Haematology*: ↑ proportion of immature reticulocyte fractions females (38% HFR, non-significant). *Blood biochemistry*: ↑ total cholesterol 32.0% females; ↑ triglycerides 23.4% females; ↑ Na 2.5% females; ↓ albumin 7.2% females; ↑ alpha-1 globulin 9.1% females. *Organ weights*: ↑ 13.4%, 14.4% liver to body weight ratios in males and females respectively. *Histopathology*: 8/10 males and 10/10 females hepatocyte hypertrophy (0/10 controls). **700 ppm (67.0 mg/kg bw/day in males and 68.3 mg/kg bw/day in females)** No effects. **100 ppm (9.5 mg/kg bw/day in males and 10.0 mg/kg bw/day in females)** No effects. **NOAEL**: 700 ppm (67.0 mg/kg bw/day in males and 68.3 mg/kg bw/day in females). **LOAEL** 3000 ppm (294.8 mg/kg bw/day in males and 304.0 mg/kg bw/day in females) - target organ: liver (clinical chemistry changes, increased weight, hepatocellular hypertrophy), red blood cell parameters (lower MCHC, compensatory erythropoietic activity)	
28 day repeated dose oral (gavage) toxicity study OECD 407 (1981) GLP: Yes Rat: Tif: RAIf, (SPF) 10/sex/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 30, 150, and 750/350 mg/kg bw/day in 0.5% aqueous carboxymethylcellulose (CMC) in 0.1% Tween 80	**750/350 mg/kg bw/day** *Mortality*: At 750 mg/kg bw/day 3/10 males and 1/10 females found dead days 2 or 5. 1/10 females was sacrificed in moribund condition on day 2. No mortality at 350 mg/kg bw/day. *Clinical observations*: At 750 mg/kg bw/day creeping movement 8/10 males; hypoactive 5/10 females; hunch-backed 3/10 females. *Body weight gain*: ↓ 9.1% males to week 4. *Food consumption*: ↓ 4.6% males cumulative week 1- 4. No clinical signs at 350 mg/kg bw/day. *Haematology*: ↓ red cell parameters females (8.8% RBC, 7.0% Hb), ↑ reticulocytes females value 0.039 (control 0.026). *Blood biochemistry*: ↑ 11.5%, 10.2% globulin males and females respectively; ↑ 6.5% total protein males; ↓ 8.4% A:G ratio females; ↑ 39.1% ALAT activity females. *Organ weight*: ↑ 27.1%, 19.8% liver to body weight ratios in males and females respectively. *Histopathology*: 4/10 males and 8/10 females centrilobular hepatocyte hypertrophy (0/10 controls). **150 mg/kg bw/day** *Blood biochemistry*: ↑ 7.0% globulin; ↓ 5.7%	[redacted] (1993)

		A/G ratio males. **<u>30 mg/kg bw/day</u>** No effects. **NOEL:** 30 mg/kg bw/day **LOEL:** 150 mg/kg bw/day NOAEL: 150 mg/kg bw/day LOAEL: 750/350 mg/kg bw/day - target organ: liver (increased liver weight, increased liver enzyme activity, hepatocellular hypertrophy, glycogen accumulations), red blood cell parameters (lower values of red blood cell parameters, tendency to macrocytosis, compensatory erythropoietic activity)	
28 day repeated dose dietary toxicity study Dose ranging study to no specific guidelines. GLP: In the spirit of GLP, however not submitted to QA. Dog: Beagle 2/sex/group - study is considered acceptable as supplementary information only (range-finding study with only 2 dogs/sex/group)	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 500, 2000 and 4000 ppm 0, 15.28, 62.95 and 119.84 mg/kg bw/day in males; 0, 18.05, 70.24 and 118.59 mg/kg bw/day in females	**<u>4000 ppm (119.84 mg/kg bw/day in males and 118.59 mg/kg bw/day in females)</u>** *Body weight*: ↓ both sexes lost 0.25 kg over course of study (controls both sexes gained 0.4 kg). *Food consumption*: ↓ 6.8% and 22.1% over study males and females respectively. *Blood biochemistry*: ↓ 11.2% albumin males; ↓ 7.6% total protein males; ↓ 7.1% calcium males; ↓ 21.2% phosphate males; ↑ 59.4%, 69.3% alkaline phosphatase activity in males and females respectively. *Organ weight*: ↑ 26.8%, 41.8% liver to body weight ratios in males and females respectively; 34.7% kidney to body weight ratios in females; ↓ absolute (50%) and relative (48%) thymus weight in males, ↓ absolute (32%) and relative (26%) thymus weight in females. *Histopathology*: Liver hepatocyte, hypertrophy 2/2 males and 1/2 females; liver inflammatory cell infiltration 2/2 males and 2/2 females; thymus cortical atrophy, cortex 2/2 males and 1/2 females (historical control data: 0/18 in males, 1/22 in females). **<u>2000 ppm (62.95 mg/kg bw/day in males and 70.24 mg/kg bw/day in females)</u>** *Blood biochemistry*: ↓ 9.7% albumin males; ↓ 5.1% calcium males; ↓ 21.2% phosphate males; ↑ 26.4%, 59.4% alkaline phosphatase activity in males and females respectively. *Organ weight*: ↑ 22.6%, 24.7% liver to body weight ratios in males and females respectively; 30.7% kidney to body weight ratios in females; ↓ absolute (41%) and relative (43%) thymus weight in 1/2 male. *Histopathology*: Liver hepatocyte, hypertrophy 1/2 males and; liver inflammatory cell infiltration 1/2 males. **<u>500 ppm (15.3 mg/kg bw/day in males and 18.1 mg/kg bw/day in females)</u>** No effects.	[redacted] (1993)

		NO(A)EL: 500 ppm (15.3 mg/kg bw/day in male and 18.1 mg/kg bw/day in females). **LO(A)EL**: 2000 ppm (63.0 mg/kg bw/day in males and 70.24 mg/kg bw/day in females) - target organ: liver (ALP increase, increased weight, hepatocellular hypertrophy), thymus (lower weight, cortical atrophy)	
90 day repeated dose dietary toxicity study OECD 408 GLP: Yes Rat: Tif: RAIf, (SPF) 10/sex/group high dose and control extra groups recovery after 1 month	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 30, 1000 and 6000 ppm 0, 2.21, 71.7 and 449.4 mg/kg bw/day in males; 0, 2.21, 76.0 and 457.4 mg/kg bw/day in females	**<u>6000 ppm (equivalent to 449.4 mg/kg bw/day in males and 457.4 mg/kg bw/day in females)</u>** *Body weight gain*: ↓ 18.2% males and 10.7% females weeks 1-14. *Food consumption*: ↓ 12.1% and 6.3% weeks 1-13 males and females respectively. *Blood biochemistry*: ↑ total protein 3.9% males, 6.4% females; ↑ globulin 5.6% males, 11.3% females; ↑ cholesterol levels 21.7% males, 32.3% females; ↓ A/G ratio 7.8% females; ↑ gamma-glutamyl transpeptidase activities 16-fold in males and 3.7-fold in females. Recovered after 4 weeks discontinuation of treatment. *Organ weight*: ↑ 13.1%, 20.6% relative liver weights in males and females respectively; ↑ 15.7%, 8.6% relative kidney weights in males and females respectively. *Histopathology*: Liver hepatocyte, hypertrophy 5/10 males and 3/10 females (0/10 controls). **<u>1000 ppm (equivalent to 71.7 mg/kg bw/day in males and 76.0 mg/kg bw/day in females)</u>** *Blood biochemistry*: ↑ total protein 5.2% females; ↑ globulin 8.7% females. **<u>30 ppm (equivalent to 2.21 mg/kg bw/day in both sexes)</u>** No effects. **NOEL:** 30 ppm (2.21 mg/kg bw/day in males and females) **LOEL**: 1000 ppm (71.7 mg/kg bw/day in males, 76.0 mg/kg bw/day in females) NOAEL: 1000 ppm (71.7 mg/kg bw/day in males, 76.0 mg/kg bw/day in females) LOAEL: 6000 ppm (equivalent to 449.4 mg/kg bw/day in males and 457.4 mg/kg bw/day in females) - target organ: liver (clinical chemistry, weight, hepatocellular hyperthrophy)	[redacted] (1994)
90 day repeat dose dietary toxicity study OECD 408 (1981), adapted to	Dimethachlor (CGA17020) technical Batch: OP. 110001	**<u>7000 ppm (equivalent to 1228 mg/kg bw/day in males and 1296 mg/kg bw/day in females)</u>** *Body weight gain:* ↓ 19.7% males weeks 1-	[redacted] (1999)

the purpose of range finding study GLP: Yes Mouse: Ico:CD1 (Crl) 10/sex/group	Purity: 96.8 % w/w 0, 100, 1000, 3500 and 7000 ppm 0, 17.5, 175, 614 and 1228 mg/kg bw/day in males; 0, 18.5, 185, 648 and 1296 mg/kg bw/day in females	14. *Organ weight*: ↑ 27.1%, 27.0% relative liver weights in males and females respectively; ↑ 38.5%, 14.4% relative kidney weights in males and females respectively. *Histopathology*: Liver hepatocyte, hypertrophy 9/9 males and 10/10 females (controls 3/10 both sexes); kidney acute tubular lesion 9/10 male (control 0/10) and female 5/10 (control 1/10). **3500 ppm (equivalent to 614 mg/kg bw/day in males and 648 mg/kg bw/day in females)** *Organ weight*: ↑ 17.1%, 10.3% relative liver weights in males and females respectively; ↑ 28.3%, 9.4% relative kidney weights in males and females respectively. *Histopathology*: Liver hepatocyte, hypertrophy 7/10 males and 9/10 females (controls 3/10 both sexes); kidney acute tubular lesion 5/10 male (control 0/10). **1000 ppm (equivalent to 175 mg/kg bw/day in males and 185 mg/kg bw/day in females)** *Organ weight*: ↑ 12.3% Relative liver weights males; ↑ 11.9%, 11.0% relative kidney weights in males and females respectively. *Histopathology*: Liver hepatocyte, hypertrophy 7/10 males (controls 3/10). **100 ppm (equivalent to 17.5 mg/kg bw/day in males and 18.5 mg/kg bw/day in females)** No effects. **NOEL**: 100 ppm (17.5 mg/kg bw/day in males and 18.5 mg/kg bw/day in females). **LOEL:** 1000 ppm (175 mg/kg bw/day in males and 185 mg/kg bw/day in females) **NOAEL**: 1000 ppm (175 mg/kg bw/day in males and 185 mg/kg bw/day in females) **LOAEL**: 3500 ppm (614 mg/kg bw/day in males and 648 mg/kg bw/day in females) - target organ: liver (increased weight, hepatocellular hypertrophy), kidney (increased weight, acute tubular lesion)	
90 day repeat dose dietary toxicity study Predates GLP and test guidelines Dog: Beagle 5/sex (control and high dose) or 4/sex other groups 1 male and female from high dose and control groups	Dimethachlor (CGA17020) technical Batch: P12 Krist 1.74 Purity: 93.8% w/w 0, 100, 350 and 1250 ppm 0, 3.4, 10.1 and 35.4 mg/kg bw/day in males; 0, 3.1, 10.4, 45.4	**1250 ppm (equivalent to 35.4 mg/kg bw/day in males and 45.4 mg/kg bw/day in females)** *Blood biochemistry:* ↑ Alkaline phosphatase activity 83.5%, 89.2% in males and females respectively week 9. Recovered after 4 weeks discontinuation of treatment. *Organ weight*: ↑ 23.1% absolute liver weights females. *Histopathology*: Liver concentric laminated cytoplasmic inclusions in hepatocytes 4/4	[redacted] (1974)

kept on recovery for 1 month	mg/kg bw/day in females	males and 2/4 females (0/4 controls). **<u>350 ppm (equivalent to 10.1 mg/kg bw/day in males and 10.4 mg/kg bw/day in females)</u>** No effects. **<u>100 ppm (equivalent to 3.4 mg/kg bw/day in males and 3.1 mg/kg bw/day in females)</u>** No effects. **NOEL**: 350 ppm (10.1 mg/kg bw/day in males and 10.4 mg/kg bw/day in females). **LOEL:** 1250 ppm (35.4 mg/kg bw/day in males and 45.4 mg/kg bw/day in females) NOAEL: ≥1250 ppm (≥35.4 mg/kg bw/day in males and ≥45.4 mg/kg bw/day in females) - target organ: liver (clinical chemistry, weight, concentric laminated cytoplasmic inclusions in hepatocytes)	
90 day repeat dose dietary toxicity study OECD 409 (1981) GLP: Yes Dog: Beagle 4/sex/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 300, 1000 and 3000 ppm 0, 9.96, 32.28 and 104.3 mg/kg bw/day in males; 0, 10.81, 35.95 and 102.8 mg/kg bw/day in females	**<u>3000 ppm (equivalent to 104.3 mg/kg bw/day in males and 102.8 mg/kg bw/day in females)</u>** *Body weight*: Males lost 0.45 kg to week 13 (controls gained 0.7 kg). *Haematology*: ↓ Hb 20.8%; ↓ Hct 13.6%; ↓ MCH 6.5%; ↓ MCHC 7.9% males only week 13; ↑ reticulocytes approx. 60% in both sexes week 13. *Blood biochemistry:* ↓ 5.6% males, 6.3% females total protein; ↓ 17.1% males, 9.1% females albumin levels; ↓ 24.8% males, 7.0% females A/G ratios; ↑ 68.5% males, 136.2% females alkaline phosphatase activity and ↑ 69.8% females ɣ-GT activity – all week 13. *Organ weights*: ↑ 44.6% and 28.3% relative liver weights in males and females respectively; ↑ 22.4% and 22.9% relative kidney weights in males and females respectively; ↓ 11.6% and 20.4% relative thymus in males and females respectively. *Histopathology*: Liver hepatocyte hypertrophy 3/4 males and 4/4 females (0/4 controls); ↑ hepatocellular cytoplasmic vacuolisation 2/4 females (1/4 controls); thymus 3/4 males cortical atrophy (1/4 controls). **<u>1000 ppm (equivalent to 32.28 mg/kg bw/day in males and 35.95 mg/kg bw/day in females)</u>** *Blood biochemistry:* ↓ 4.5% female total protein; ↓ 4.6% female albumin levels; ↑ 52.2% female alkaline phosphatase activity – all week 13. *Organ weights*: ↑ 17.2% and 18.7% relative liver weights in males and females	[redacted] (1994), (1994a)

		respectively. *Histopathology*: Liver hepatocyte hypertrophy 1/4 males and 1/4 females (0/4 controls); ↑ hepatocellular cytoplasmic vacuolisation 2/4 females (1/4 controls). **<u>300 ppm (equivalent to 9.96 mg/kg bw/day in males and 10.81 mg/kg bw/day in females)</u>** *Organ weights*: ↑ 17.2% relative liver weights in females. **NOAEL**: 300 ppm (9.96 mg/kg bw/day in males and 10.81 mg/kg bw/day in females) **LOAEL:** 1000 ppm (equivalent to 32.28 mg/kg bw/day in males and 35.95 mg/kg bw/day in females) - target organ: liver (clinical chemistry changes, increased weight, hepatocellular hyperthrophy and cytoplasmic vacuolisation), red cell parameters	

Carcinogenicity Study OECD 453 (1981). GLP: Yes Rat: Tif:RAIf (SPF) 50/sex/group for carcinogenicity 10/sex/group for one year interim kill 10/sex/group for haematological, biochemical and urine analysis, 10/sex/group for haematological investigations	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: diet 0, 20, 300, 4000 ppm 0, 0.765, 11.1 and 157.3 mg/kg bw/day in males; 0, 0.892, 12.9, and 182.6 mg/kg bw/day in females For 24 months	**Non-neoplastic findings** **4000 ppm (157.3 mg/kg bw/day in males, 182.6 mg/kg bw/day in females)** ↑ *Survival*: 72% in both sexes after 104 weeks, controls 48% in males and 52% in females. ↓ *Body weight gain:* up to 11.6% in males (week 75) and 15.2% in females (week 103). ↓ *Food consumption*: males mainly during the first three months, females throughout the first year and sporadically for remainder of study. Cumulative for study 3.8% males, 8.0% females. *Haematology:* ↓ platelets in males max. 12% week 105, 14% in females; ↑ prothrombin time in males in first year of treatment maximum 29% week 13. *Blood biochemistry*: ↑ gamma-glutamyl transpeptidase activity males 14.5 times control week 52, 3 times control week 105. *Organ weights*: ↑ Relative liver 9.4% males week 105, 19.5% females week 53; ↑ Absolute kidney 8.1% males week 105, ↑ Relative kidney 22.2% males, 14.2% females week 105. *Histopathology*: Hepatocyte hypertrophy 24/60 males, 17/60 females (0/60 controls); Liver cytoplasmic inclusion bodies 27/60 males (0/60 controls). **300 ppm (11.1 mg/kg bw/day in males, 12.9 mg/kg bw/day in females)** No effects. **20 ppm (0.765 mg/kg bw/day in males, 0.892 mg/kg bw/day in females)** No effects. **Neoplastic findings** No overall increase in tumour incidence. Following extensive histopathological examination at 4 different levels of the respiratory epithelium of the nasopharynx a slightly increased incidence of adenoma of the respiratory epithelium in 3 high dose males (3/60; control group: 0/60) was observed. **NOAEL for chronic toxicity:** 300 ppm (11.1 or 12.9 mg/kg body weight per day for males and females, respectively) **LOAEL for chronic toxicity**: 4000 ppm (157.3 mg/kg bw/day in males, 182.6 mg/kg bw/day in females)	[redacted] & [redacted] (1995)

		NOAEL for carcinogenicity: 300 ppm (11.1 or 12.9 mg/kg body weight per day for males and females, respectively) **LOAEL for carcinogenicity**: 4000 ppm (157.3 mg/kg bw/day in males, 182.6 mg/kg bw/day in females) - target organs: liver (increased liver weight, cytoplasmatic inclusion bodies, hepatocyte hypertrophy, increased gamma-glutamyl transpeptidase activity), kidney (increased kidney weight), nasopharynx (adenoma).	
Carcinogenicity Study OECD 451 (1981) GLP: Yes Mouse: Tif: MAGf, (SPF) 50/sex/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 20, 300 and 4000 ppm 0, 2.25, 32.3 and 488.1 mg/kg bw/day in males; 0, 2.17, 31.2 and 450.9 mg/kg bw/day in females For 18 months	**Non-neoplastic findings** **4000 ppm (488.1 mg/kg bw/day in males, 450.9 mg/kg bw/day in females)** ↓ *Body weight*: 9.7% and 10.0% in males and females respectively week 77. *Organ weights*: ↑ 17.1%, 12.2% liver to body weight ratios in males and females respectively; ↑ 41% and 20.9% kidney to body weight ratios in males and females respectively. *Histopathology*: hepatocyte hypertrophy 45/50 males (25/50 controls), 46/50 females (27/50 controls); 25/50 males renal chronic progressive nephropathy (control 3/50), 16/50 males renal tubular dilatation (control 2/50) and 33/50 renal cysts (control 16/50). **300 ppm (32.3 mg/kg bw/day in males, 31.2 mg/kg bw/day in females)** *Organ weights*: ↑ 16.2% kidney to body weight ratios in males. **20 ppm (2.25 mg/kg bw/day in males, 2.17 mg/kg bw/day in females)** No effects. **NOAEL for chronic toxicity**: 300 ppm (32.3 mg/kg bw/day for males and 31.2 mg/kg bw/day in females). **LOAEL for chronic toxicity**: 4000 ppm (488.1 mg/kg bw/day in males, 450.9 mg/kg bw/day in females) **NOAEL for carcinogencitiyty**: 4000 ppm (488.1 mg/kg bw/day in males, 450.9 mg/kg bw/day in females) - target organ: kidney (increased incidence and severity of kidney changes (chronic progressive nephropathy, renal tubular dilatation and renal cysts in males, and renal tubular atrophy in females), liver (hepatocellular hypertrophy, increased relative liver weights, benign liver tumours in high dose males within the range of historical control data)	[redacted] (1995)
Carcinogenicity Study OECD 451 (1981). GLP: Yes	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w	**Non-neoplastic findings** **4000 ppm (511 mg/kg bw/day in males, 454 mg/kg bw/day in females)** ↓ *Body weight*: 8.0% males week 78. ↓ *Body weight gain*: males 29.5% weeks 1-	[redacted] (2001)

Mouse: albino (ICO:CD1 (Crl)) 50/sex/group for carcinogenicity 10/sex/group for 9 month interim kill 10/sex/group for haematology	Vehicle: diet 0, 20, 300, 1500, 4000 ppm 0, 2.54, 34.3, 184 and 511 mg/kg bw/day in males; 0, 2.25, 31.4, 162 and 454 mg/kg bw/day in females For 18 months	13, 25.2% weeks 1-78. ↓ *Food utilisation efficiency*: males 35.2% weeks 1-12. *Organ weights:* ↑ Relative kidney males 32.9% week 40, 43.8% week 79-81; ↑ Relative liver 19.7% males, 22.0% females week 79-81. *Histopathology:* perilobular hepatocyte hypertrophy 35/50 males, 46/50 females (0/50 controls); chronic nephropathy 15/50 males (0/50 controls). **1500 ppm (184 mg/kg bw/day in males, 162 mg/kg bw/day in females)** ↓ *Body weight*: 6.15% males week 78. ↓ *Body weight gain*: males 20.9% weeks 1-13, 20.4% weeks 1-78. ↓ *Food utilisation efficiency*: males 24.7% weeks 1-12. *Organ weights:* ↑ Relative kidney males 18.0% week 40, 25.6% week 79-81; ↑ Relative liver 13.5% males, 11.7% females week 79-81. *Histopathology:* perilobular hepatocyte hypertrophy 20/50 males, 38/50 females (0/50 controls); chronic nephropathy 7/50 males (0/50 controls). **300 ppm (34.3 mg/kg bw/day in males, 31.4 mg/kg bw/day in females)** *Organ weights:* ↑ Relative kidney males 8.0% 79-81. *Histopathology:* kidney atrophy tubular 35/50 males (25/50 controls), 21/50 females (16/50 controls). **20 ppm (2.54 mg/kg bw/day in males, 2.25 mg/kg bw/day in females)** No effects. **NO(A)EL for chronic toxicity:** 20 ppm (2.54 mg/kg bw/day in males, 2.25 mg/kg bw/day in females) **LO(A)EL for chronic toxicity:** 300 ppm (34.3 mg/kg bw/day for males, 31.4 mg/kg bw/day for females) No increase in tumour incidence. **NOEL for carcinogenicity:** 4000 ppm (511 mg/kg bw/day in males, 454 mg/kg bw/day in females). - target organs: kidney (chronic progressive nephropathy in males and renal tubular atrophy in females, increased kidney weights in males and females), liver (hepatocellular hypertrophy and increased liver weights and/or ratios in male and female)	
Repeat dose dermal toxicity study OECD 410 (1981)	Dimethachlor (CGA17020) technical Batch: OP.	**1000 mg/kg bw/exposure** No effects.	[redacted] (1993d)

GLP: Yes Rat: Tif: RAIf, (SPF) 5/sex/group	110001 Purity: 96.8% w/w 0, 10, 100 and 1000 mg/kg bw/exposure 6 hours per day, 5 days per week for 4 weeks	**100 mg/kg bw/exposure** No effects. **10 mg/kg bw/exposure** No effects. **NOEL**: ≥ 1000 mg/kg bw/exposure. **NOAEL: > 1000 mg/kg bw/exposure**	

Table 38: Summary table of human data on repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 39: Summary table of other studies relevant for repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of study/data	Test substance	Observations	Reference
Reproductive toxicity Two generations / two F1 litters, one F2 litter OECD 416, 1983 (deviations from OECD 416, 2001) GLP Rat, Sprague-Dawley Crl:CD (SD)BR strain 25/sex/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 20, 300, 2000 and 4000 ppm Continuous in the diet 0, 20, 300, 2000, 4000 ppm (0, 1.33, 20, 133 and 267 mg/kg bw/day)	***Parental toxicity*** **4000 ppm:** **F0 (Pre-mating: 222-399 mg/kg bw/day males, 256-415 mg/kg bw/day females)** ↓ body weight gain (not significant) pre-mating (males 13% days 1-8, 9% days 1-99; females 14% days 1-8, 11% days 1-99); ↓ food consumption females (1st pre-mating 8% days 1-8, 1st gestation 5-9% not significant; 1st lactation from day 4 3-8% not significant; 2nd pre-mating 10% not significant; 2nd lactation max. 12% days 14-21 not significant). **F1 (Pre-mating: 237-443 mg/kg bw/day males, 285-463 mg/kg bw/day females)** ↓ body weight gain (not significant) pre-mating (males 11% days 1-99; females 10% days 1-99); ↓ food consumption females (pre-mating 8% days 1-99, gestation 15% days 0-7, lactation from day 4 8-12%). **2000 ppm:** **F0 (Pre-mating: 105-200 mg/kg bw/day males, 122-218 mg/kg bw/day females)** ↓ food consumption females (1st lactation days 14-21 14% not significant; 2nd lactation days 14-21 15%). **F1 (Pre-mating: 110-219 mg/kg bw/day males, 137-232 mg/kg bw/day females)** ↓ body weight gain pre-mating (males 13% days 1-99, not significant); ↓ food consumption females (pre-mating 6% days 1-99, gestation 13% days 0-7, lactation from day 4 5-7%, not significant). **300 ppm:** **F0 (Pre-mating: 15-32 mg/kg bw/day males, 18-33 mg/kg bw/day females)** No effects.	[redacted] (1994)

		F1 (Pre-mating: 16-34 mg/kg bw/day males, 21-36 mg/kg bw/day females) No effects. ***Reproduction toxicity*** **<u>4000 ppm</u>** No effects. ***Offspring*** [Unusually high F1a pup loss between 7-14 for F1a litters in control and treated groups. A reason for this finding could not be detected so it was considered incidental and a reflection of the biological variability within this species] **<u>4000 ppm</u>** **F1 litters** ↓ body weight day 21 (systemic, not lactation effect) (F1a males 13% not significant, females 12%; F1b males 14% males, 16% females). **F2 litters** ↓ body weight day 21 (systemic, not lactation effect) (F2a males 19%, females 18%). **<u>2000 ppm</u>** **F1 litters** ↓ body weight day 21 (systemic, not lactation effect) (F1a males 17%, females 4%, not significant; F1b males 11% males not significant, 11% females). **F2 litters** ↓ body weight day 21 (systemic, not lactation effect) (F2a males 13%, females 11%). **<u>300 ppm</u>** No effects. **NOAEL:** Parental: 300 ppm (20 mg/kg/day) Reproduction/fertility: 4000 ppm (267 mg/kg/day) Offspring: 300 ppm (20 mg/kg/day) **LOAEL**: Parental: 2000 ppm (133 mg/kg bw/day) Reproductive/fertility: >4000 ppm (> 267 mg/kg bw/day) Offspring: 2000 ppm (133 mg/kg bw/day)	
Developmental toxicity OECD 414 1981; short dosing period cf. OECD 414, 2018 GLP Rat, Tif: RAI f strain 25 mated females/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 50, 350, 700 mg/kg bw/day by oral gavage on gestation days 6-15 Vehicle 0.5% CMC	***Maternal toxicity*** **<u>700 mg/kg bw/day</u>:** 5/25 deaths gestation days 9-14; 1/5 found dead day 9, 4/5 moribund having exhibited convulsions, dyspnea and/or hunched posture, piloerection; ↓ body weight gain (29%, days 6-11, 17% days 6-16); ↓ food consumption (15% days 6-11, 9% days 11-16). **<u>350 mg/kg bw/day</u>:** ↓ food consumption (11% days 6-11; 6% days 11-16 not significant).	[redacted] (1994)

		50 mg/kg bw/day: No effects. ***Developmental toxicity*** **700 mg/kg bw/day:** ↑ skeletal anomalies: 53% litters cf. 25% controls due to ↑ wide fontanel (2% foetal & 16% litter incidence cf. 0% controls - HCD range 0-0.6% and 0-4.3% respec.); ↑ irregular ossification of occipital bone (2% foetal & 16% litter incidence cf. 0% controls - HCD range 0-0.9% and 0-6.3% respec.); ↑ bipartite occipital bone (1.5% foetal & 5% litter incidence cf. 0% controls – no HCD range reported); ↑ skeletal variations: reduced ossification or absence of phalangeal bones – foetal & litter incidences higher than HCD. **350 mg/kg bw/day:** ↑ skeletal anomalies: 50% litters cf. 25% controls due to ↑ wide fontanel (1% foetal & 4% litter incidence cf. 0% controls - HCD range 0-0.6% and 0-4.3% respec.); ↑ irregular ossification of occipital bone (1% foetal & 8% litter incidence cf. 0% controls - HCD range 0-0.9% and 0-6.3% respec.); ↑ skeletal variations: reduced ossification or absence of phalangeal bones – foetal & litter incidences higher than HCD. **50 mg/kg bw/day:** No effects. **NOAEL:** Maternal: 50 mg/kg/day Foetal: 50 mg/kg/day **LOAEL**: Maternal: 350 mg/kg/day Foetal: 350 mg/kg/day No evidence for teratogenicity.	
Developmental toxicity OECD 414 1981; short dosing period cf. OECD 414, 2018 GLP Rabbit, NZW strain 20 inseminated females/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 10, 100, 350, 600 mg/kg bw/day by oral gavage on gestation days 6-18 Vehicle 1.5% MC	***Maternal toxicity*** **600 mg/kg bw/day:** 3/3 deaths: 1/3 dead after one dose, 1/3 after two doses, 1/3 killed after two doses. No further animals allocated to group. **350 mg/kg bw/day:** 2/20 dead gestation days 18-20 (mortalities were considered by the study authors to be incidental), 1/20 aborted day 22; ↓ body weight loss days 6-9 (-47%); ↓ body weight gain (35% days 6-19); ↓ food consumption (32% days 6-9, 18% days 9-12). **100 mg/kg bw/day:** No effects (1/20 animal was found dead on gestation day 18, but this mortality was considered to be incidental). ***Developmental toxicity*** **350 mg/kg bw/day:** No treatment-related effects.	[redacted] (1993)

		[↑ pre-implantation loss (43% cf. 23.5% controls) incidental to treatment but resulting in ↓ number live foetuses (5.5 cf. 8.4 controls) and ↓ litter weight (35%) due to fewer foetuses. Also, high incidence of malformation in all groups including control; no effect of treatment indicated.] **NOAEL**: Maternal: 100 mg/kg/day Foetal: 350 mg/kg/day **LOAEL**: Maternal: 350 mg/kg/day Foetal: not determined No evidence for teratogenicity.	

2.6.3.2 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure (short-term and long-term toxicity)

Summary of short-term toxicity

Oral short-term toxicity studies with dimethachlor were performed in rats, mice and dogs, and dermal in rats. Also, one long-term study in rats, two long-term studies in mice, 2-generation study in rats, and two developmental studies, one in rats and another in rabbits, were evaluated for repeated dose toxicity. All these studies have been evaluated in the original DAR (2007).

Dimethachlor is generally of low toxicity in all species tested in repeat dose studies. Although there are 28-day studies in three species, the key studies are considered the 90-day studies.

There were small changes in body weight gain and food consumption, but these do not indicate significant toxicity.

There is a consistent pattern of toxicity in rats, mice and dogs fed dimethachlor in the diet for 90 days ([redacted], 1994; [redacted], 1999 and [redacted] 1994). The target organ is identified as the liver and changes are characterised by altered clinical chemistry values (decreases in globulin, total protein, A/G ratio and cholesterol and increased activity of alkaline phosphatase and ɣ-GT). These clinical chemistry changes are accompanied by increased absolute and relative liver weights and histopathology findings of hepatocyte hypertrophy.

The results of the 90-day rat study ([redacted], 1994) indicate that the changes in clinical chemistry were no longer evident after a 4-week recovery phase. The effects and no effect levels are rather similar in the three species examined. The findings relating to the liver are considered to represent a normal response to the administration of a xenobiotic substance, they are considered an adaptive response, and none is of sufficient severity to be considered specific target organ toxicity. There is no evidence in any of the key studies of marked organ dysfunction in the liver.

In one 90-day dog study ([redacted], 1994), there was evidence of effects on red cell parameters at the top dose level (3000 ppm; 104 and 103 mg/kg bw/day in males and females respectively). There were no similar findings in the rat or the mouse or in an earlier study in the do[redacted]1974). Although there was a marked decrease in haemoglobin, haematocrit and MCH and MCHC in males, there were no similar findings in females. The anaemia was only seen in animals where there was a reduction in body weight over the 13-week course of the study. Both sexes showed an increase in reticulocytes which is considered to demonstrate regenerative anaemia. There was no evidence of the histopathological findings that might be expected to accompany severe anaemia (i.e. haemosiderosis in the spleen, liver or kidney) and therefore the effects seen are considered not to represent significant target organ toxicity. Atrophy of the thymus was observed in two dog studies ([redacted], 1993 and 1994) at the top dose levels (4000 ppm and 3000 ppm respectively). These dose levels were also associated with body weight loss. At such dose levels an atrophy of the thymus can be considered as secondary to physiological stress at a toxic dose.

In all three species higher dose levels caused an increase in the kidney weight. There were histopathological findings in the kidney in three mouse studies ([redacted], 1999; [redacted], 1995; [redacted], 2001). In the 90-day study ([redacted], 1999) the incidence of renal acute tubular lesions was increased in males from 614 mg/kg bw/day and females from 1296 mg/kg bw/day (no renal effects observed at 175 mg/kg bw/day). The lesion consisted of swelling and slight vacuolisation of tubular epithelium and dilated renal tubules with eosinophilic material in the tubular lumen (without degenerative changes). There were no histopathology findings in the kidneys of animals in any of the other studies of 28 or 90 days duration. In the 18 month mouse carcinogenicity study ([redacted], 1995) there was an increased incidence of renal chronic progressive nephropathy and renal tubular dilatation in the males only.

This occurred at a dose level of 488.1 mg/kg bw/day. In the second carcinogenicity study in mice ([redacted], 2001), chronic nephropathy in males was observed at 511 mg/kg bw/day, and kidney tubular atrophy in males at 34.3 mg/kg bw/day and in females at 31.4 mg/kg bw/day. There were no effects on kidney at the lowest dose (2.54 and 2.25 mg/kg bw/day in males and females, respectively).

There were no findings in a 28 day repeat dose dermal study in rats ([redacted], 1993).

In developmental study in rats [redacted]1994), mortality of was observed at 700 mg/kg bw/day. One high dose animal was found dead on day 9 p.c. and four high dose animals were sacrificed moribund on days 9, 11 and 14 p.c. (i.e. after at 3 - 8 days of treatment). Treatment-related clinical signs were observed in these animals. In developmental study in rabbits ([redacted] 1993), out of three animals treated at 600 mg/kg bw/day, two were found dead, one after the 1st dose, and second animal after the second dose. The third animal was killed. The animals were not pregnant. At the lower dose, 350 mg/kg bw/day, two animals died at the end of the treatment period (after 12th or 13th dose). Body weight loss and decreased body weight gain were also observed at that dose. No maternal toxicity was observed at the lowest dose tested, 100 mg/kg bw/day.

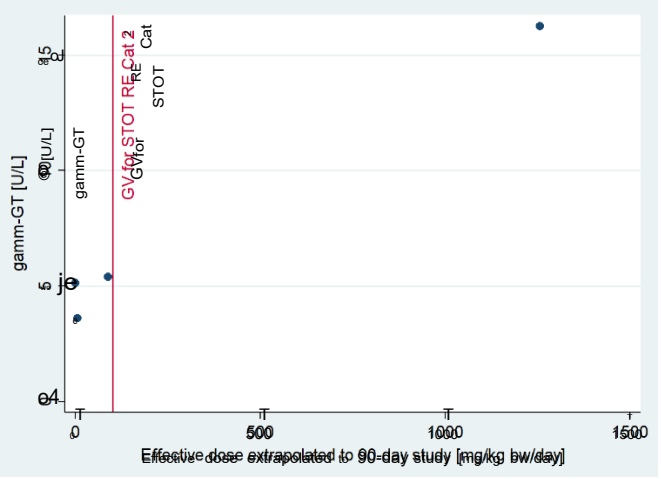
Table 40: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days

Study reference	Effective dose (mg/kg bw/day) (males/females)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
[redacted] (1992b)	NOEL: 20.9 / 23.2 LOEL: 204 / 232 NOAEL: 204 / 232 LOAEL: 624 / 715	28 days	NOEL: 7.0 / 7.7 LOEL: 68.1 / 77.4 NOAEL: 68 / 77.3 LOAEL: 208 / 238	No
[redacted] (1992a)	NOAEL: 67.0 / 68.3 LOAEL: 295 / 304	25/26 days	NOAEL: 22.3 / 22.8 LOAEL: 83.6 / 86.1	No
[redacted] (1993)	NOEL: 30 / 30 LOEL: 150 /150 NOAEL: 150 LOAEL: 350	28 days	NOEL: 10 / 10 LOEL: 50 / 50 NOAEL: 50 LOAEL: 116.7	No
[redacted] (1993)	NO(A)EL: 15.3/18.1 LO(A)EL: 63.0/70.2	28 days	NO(A)EL: 5.1 / 6.0 LO(A)EL: 21.0/23.4	No
[redacted] (1994)	NOEL: 2.21 / 2.21 LOEL: 71.7 / 76.0 NOAEL: 71.7 / 76 LOAEL: 449 / 457	90 days	NOEL: 2.21 / 2.21 LOEL: 71.7 / 76.0 NOAEL: 71.7 / 76 LOAEL: 449 / 457	No
[redacted] (1999)	NOEL: 17.5 / 18.5 LOEL: 175 / 185 NOAEL: 175 / 185 LOAEL: 614 / 648	90 days	NOEL: 17.5 / 18.5 LOEL: 175 / 185 NOAEL: 175 / 185 LOAEL: 614 / 648	No
[redacted] (1974)	NOEL: 10.1 / 10.4 LOEL: 35.4 / 45.4 NOAEL: ≥35.4 / ≥45.4 LOAEL: ND	90 days	NOEL: 10.1 / 10.4 LOEL: 35.4 / 45.4 NOAEL: ≥35.4 / ≥45.4 LOAEL: ND	No
[redacted] (1994)	NOAEL: 9.96 / 10.8 LOAEL: 32.3 / 36.0	90 days	NOAEL: 9.96 / 10.8 LOAEL: 32.3 / 36.0	No
[redacted] & (1995)	NO(A)EL: 11.1/12.9 LO(A)EL: 157 / 183	24 months	NO(A)EL: 88.8/103 LO(A)EL: 1258/1461	No
[redacted] (1995)	NOAEL: 32.3 / 31.2 LOAEL: 488 / 451	18 months	NOAEL: 194 / 187 LOAEL: 2928 /2706	No
[redacted] (2001)	NO(A)EL: 2.54 / 2.25 LO(A)EL: 34.3 / 31.4	18 months	NO(A)EL: 15.2 / 13.5 LO(A)EL: 206 / 188	No
[redacted] (1994)	$NOAEL_{Parental}$: 20 $LOAEL_{Parental}$: 133	2 generation	$NOAEL_{Parental}$: 20 $LOAEL_{Parental}$: 133	No
[redacted] (1994)	$NOAEL_{Maternal}$: 50 $LOAEL_{Maternal}$: 350 $LOAEL_{Maternal\ mortality}$: 700	10 days	$NOAEL_{Maternal}$: 5.6 $LOAEL_{Maternal}$: 38.9 $LOAEL_{Maternal\ mortality}$: 77.8	(Yes)
[redacted] (1993)	$NOAEL_{Maternal}$: 100 $LOAEL_{Maternal}$: 350	13 days	$NOAEL_{Maternal}$: 14.4 $LOAEL_{Maternal}$: 50.6	(Yes)

Study reference	Effective dose (mg/kg bw/day) (males/females)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
	$LOAEL_{Maternal\ mortality}$: 600		$LOAEL_{Maternal\ mortality}$: 86.7	

ND: not determined

[redacted] & [redacted] (1995), gamma-GT in males, week 105:



2.6.3.1.2 Comparison with the CLP criteria regarding STOT RE (specific target organ toxicity-repeated exposure)

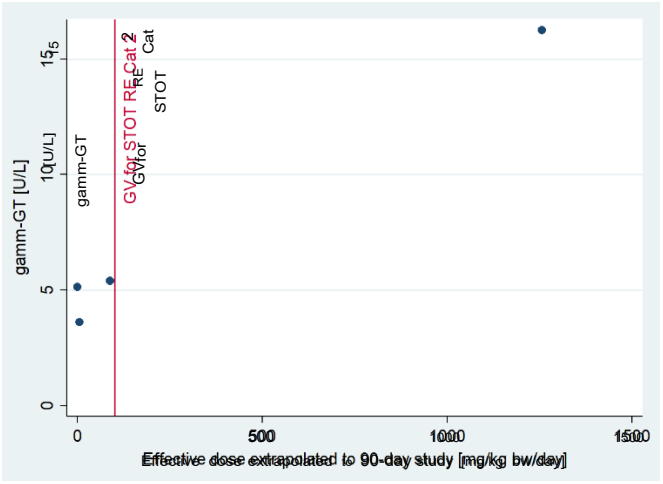
According to the CLP regulation classification in STOT RE is required for substances that cause: "… consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ or have produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health."

Substances are classified as specific target organ toxicants following repeated exposure based on "significant" or "severe" toxicity. In this context "significant" means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. "Severe" effects are generally more profound or serious than "significant" effects and are of a considerably adverse nature which significantly impact on health. In general, valid data from animal experiments are considered relevant for humans and are used for hazard assessment/classification. However, it is acknowledged that there are cases where animal data are not relevant for humans and should not be used for that purpose.

The effects of dimethachlor following repeated dosing included general non-specific effects on body weight and food consumption. These effects do not, by themselves, indicate "significant toxicity". Therefore, these findings were not considered to justify classification.

The target organ is identified as the liver and changes are characterised by altered clinical chemistry values (decreases in globulin, total protein, A/G ratio and cholesterol and increased activity of alkaline phosphatase and ɣ-GT). These clinical chemistry changes are accompanied by increased relative liver weights and histopathology findings of hepatocyte hypertrophy. There is no evidence of organ dysfunction. The changes are adaptive responses, and show recovery when dosing is stopped, and are considered not to be evidence of significant target organ toxicity. Therefore, these findings were not considered to justify classification. Even if increased gamma-GT activity (up to 14.5 times at week 52) and increased incidence of liver cytoplasmic inclusion bodies in males in [redacted] & [redacted] (1995) carcinogenicity study are considered as potentially toxicologically relevant, dose level at which these effects were observed is well above guidance value for STOT RE Category 2 (please see Figure below).

[redacted] & [redacted] (1995), gamma-GT in males, week 105:



The LOAEL values (extrapolated to 90-day exposure, where required) were within the guidance range for STOT RE Category 2 classification (10 < C ≤ 100 mg/kg bw/day) in 25/26-day study in rats (83.6 and 86.1 mg/kg bw/day in males and females, respectively) ([redacted], 1992a), 28-day study in dogs (21.0 and 23.4 mg/kg bw/day in males and females, respectively) ([redacted], 1993), 3-month study in dogs (32.3 and 36.0 mg/kg bw/day in males and females, respectively) ([redacted], 1994), and developmental studies in rats (maternal LOAEL: 38.9 mg/kg bw/day; LOAEL for maternal mortality: 77.8 mg/kg bw/day) [redacted]1994) and rabbits (maternal LOAEL: 50.6 mg/kg bw/day; LOAEL for maternal mortality: 86.7 mg/kg bw/day) ([redacted]1993).

In 25/26-day study in rats ([redacted], 1992a), at LOAEL of 83.6 mg/kg bw/day in males and 86.1 mg/kg bw/day in females (values extrapolated to 90-day exposure), increased total cholesterol and triglyceride concentrations were observed in female rats and increased liver weight and hepatocellular hypertrophy in both sexes. Nevertheless, these changes were not considered to be severe enough to trigger STOT RE classification. Increased total cholesterol (by 32% compared to controls) and triglyceride concentration (by 23%) in females were still within the historical control range. The mean liver to body weight ratio was increased by 13% in males and by 14% in females, and hepatocellular hypertrophy was minimal to slight. Therefore, described liver changes were considered to be an adaptive response to the test substance intake.

In 28-day study in dogs ([redacted], 1993), at LOAEL of 21.0 mg/kg bw/day in males and 23.4 mg/kg bw/day in females (values extrapolated to 90-day exposure), increased absolute and relative liver weights (the values within historical control range), increased alkaline phosphatase (by 26% compared to control), slightly reduced food consumption in females (with transiently decreased body weight gain), some clinical chemistry changes of unclear toxicological significance (lower albumin, urea and creatinine levels – the values were within the historical control range and/or without clear dose-response pattern), increased kidney weight in females (by 22% in absolute and 31% in relative weight), lower thymus weight in one male (without histopathological changes in these organs at this dose level), and hepatocellular hypertrophy were observed. These changes were not considered to be severe enough to trigger STOT RE classification. Increase in ALP activity was also observed, but it was not pronounced (by 26% in males and 59% in females), and in the absence of histopathological indices of liver injury could be probably regarded as an adaptive response. It should be noted that due to limitations of the study (primarily regarding a low number of animals used, i.e. 2 instead of 4 animals per sex and dose), this study is considered acceptable only as supplementary information.

In 3-month study in dogs ([redacted], 1994), at LOAEL of 32.3 mg/kg bw/day in males and 36.0 mg/kg bw/day in females, increased relative (organ to body) liver weight was observed in males (17% increase compared to control) and females (19% increase compared to control), accompanied by centrilobular hepatocellular hypertrophy and increased incidence of minimal hepatocellular cytoplasmic vacuolisation. Although the nature of vacuolisation was not further investigated, in the absence of clinical chemistry changes and more severe histopathological hepatic changes, these effects are not considered to be severe enough to trigger STOT RE classification.

In one 90-day dog study there was also evidence of effects on red cell parameters at the top dose level in males only. Both sexes showed an increase in reticulocytes which is considered to demonstrate regenerative anaemia. There was no evidence of the histopathological findings that might be expected to accompany severe anaemia and therefore the effects seen are not considered to represent significant target organ toxicity. Atrophy of the thymus was observed in two dog studies at the top dose level. These dose levels were also associated with body weight loss. At such dose levels atrophy of the thymus can be considered as secondary to physiological stress at a toxic dose. Therefore, these findings were not considered to justify classification.

Kidney weights were increased following administration of dimethachlor and these increases were associated with microscopic pathology findings in three studies in the mice. The exposure level at which these effects occurred was, however, above the guidance value for classification. Therefore, these findings were not considered to justify classification.

Mortality was observed in pregnant rats and rabbits in developmental toxicity studies at dose levels (77.8 mg/kg bw/day in rats and 86.7 mg/kg bw/day in rabbits, extrapolated to 90-day exposure) that are below guidance value for STOT RE Category 2 (100 mg/kg bw/day). According to CLP Regulation, STOT RE classification could be trigerred by "morbidity or death resulting from repeated or long-term exposure", since "morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites". Nevertheless, mortality occurred at (non-extrapolated) dose levels of 350 – 700 mg/kg bw/day, which are within dose range of 300 < ATE ≤ 2000 mg/kg bw corresponding to Category 4 for acute oral toxicity proposed for dimethachlor. It is considered, therefore, that STOT RE classification is not justified based on these observations. Other effects observed at dose levels in the guidance range for STOT RE Category 2 classification (at maternal toxicity LOAEL of 38.9 mg/kg bw/day in rats and 50.6 mg/kg bw/day in rabbits) were not considered severe enough or relevant enough to trigger the classification [e.g. 6-11% reduced food consumption in rats ([redacted]1994); body weight loss in rabbits only during the limited time period, i.e. gestation day 6 through 9, with consequent catch-up in growth ([redacted] 1993)].

It can be concluded that repeated dosing with dimethachlor produced no effects that would justify classification for STOT RE.

2.6.3.1.3 Conclusion on classification and labelling for STOT RE (specific target organ toxicity-repeated exposure)

No classification.

2.6.4 Summary of genotoxicity / germ cell mutagenicity [equivalent to section 10.8 of the CLH report template]

Table 41: Summary table of genotoxicity/germ cell mutagenicity tests *in vitro*

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
Reverse mutation test in bacteria *in vitro* OECD 471 no statistical evaluation GLP	Dimethachlor (CGA17020) technical Batch: 1710 Purity: 98.3% w/w Vehicle: DMSO	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA 1538. Concentrations selected based on a preliminary study. Concentrations for Experiments I and II: 10.0, 33.3, 100.0, 333.3, 1000.0 and 5000 µg/plate.	Negative, not mutagenic with or without metabolic activation. No cytotoxicity or precipitation at highest concentration tested. Positive controls included.	Poth (1991)
Reverse	Dimethachlor	*Salmonella*	Negative, not mutagenic with	Chang (2019)

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
mutation test in bacteria *in vitro* OECD 471 GLP	(CGA17020) Batch: 024_FORTIFIED Purity: 95.5% w/w Vehicle: DMSO	*typhimurium* strains TA 98, TA 100, TA 1535, TA 1537. *E. coli* WP2, WP2 urA Concentrations selected based on a preliminary study. Concentrations: 10.0, 33.3, 100.0, 333.3, 1000.0 and 5000 µg/plate	or without metabolic activation. No cytotoxicity or precipitation at highest concentration tested. Positive controls included.	
Gene mutation assay in mammalian cells *in vitro* OECD 476 no statistical evaluation GLP	Dimethachlor (CGA17020) technical Batch: 1710 Purity: 98.3% w/w Vehicle: DMSO	Chinese hamster V79 cells. Concentrations selected based on a preliminary study. Two sets of independent main studies. Based on the cytotoxicity data, six concentrations ranging from 2.0 to 50.0 µg/mL with and without metabolic activation.	Negative, no indication of a mutagenic activity with or without metabolic activation. Cytotoxicity at 50 µg/mL without activation. Borderline cytotoxicity at 30 µg/mL without activation and at 50 µg/mL with activation. Positive controls included.	Müllerschön (1992)
Gene Mutation Assay in Chinese Hamster V79 Cells in vitro (V79/HPRT) OECD 476 GLP	Dimethachlor (CGA17020) Batch: 024_FORTIFIED Purity: 95.5% w/w Vehicle: DMSO	Chinese hamster V79 cells. Concentrations selected based on a preliminary study. Concentrations tested were: 32.7; 65.4; 130.9; 261.8; 523.5; 1047.0; and 2094.0 µg/mL	Negative, no indication of a mutagenic activity with or without metabolic activation. Cytotoxicity was noted at 130.9 µg/mL with and without activation. Positive controls included.	Sokolowski (2019)
DNA	Dimethachlor	Hepatocytes	Negative, no indication of	Hertner (1992)

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells *in vitro* OECD 482 no deviations GLP	(CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: DMSO	from adult male Tif:RAIf (SPF) rats. Concentrations selected based on a preliminary cytotoxicity study. Original mutagenicity experiment and confirmatory experiment concentrations 0.14, 0.42, 1.25, 3.75, 7.5 and 15.0 µg/mL.	DNA damage. Cytotoxicity at 15 µg/mL in both experiments. Positive controls included.	
In vitro Mammalian Chromosome Aberration Test OECD 473 no deviations GLP	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: DMSO	Chinese hamster ovary cells (ATCC CCL61). Concentrations selected based on a preliminary cytotoxicity study. Without metabolic activation concentrations Expt. 1 (original and confirmatory) 2.93, 5.86 and 11.72 µg/mL. Expt 3 5.86, 11.72 and 23.44 µg/mL. With metabolic activation Expts 2 (original and confirmatory) and 4 46.88, 93.75 and 187.50 µg/mL.	Negative, no increase in chromosome aberrations and no evidence of a clastogenic effect with or without metabolic activation. Concentrations tested limited by cytotoxicity. Positive controls included.	Hertner (1994)
In vitro Micronucleus Test in	Dimethachlor (CGA17020) Batch: 024_FORTIFIED	Human lymphocytes Concentrations selected based	Positive, considered to be mutagenic, when tested up to cytotoxic or the highest evaluable concentration	Naumann, 2019

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
Human Lymphocytes OECD 476 GLP	Purity: 95.5% w/w Vehicle: DMSO	on a preliminary cytotoxicity study. Two main experiments ran at concentration: 13.6, 23.8, 41.7, 72.9, 128, 223, 391, 684, 1197, 2094 µg/mL	Clear cytotoxicity was observed in both experiments and the value of micronucleated cells was statistically significantly increased Positive controls included.	

Table 42: Summary table of genotoxicity/mutagenicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviation if any	Test substance	Relevant information about the study (as applicable)	Observations/Results	Reference
Micronucleus assay in bone marrow cells OECD 474 deviations: cytotoxicity of the bone marrow not shown: PCE/NCE not decreased in dimethachlor-treated animals and no toxicokinetic data in mouse were presented – no proof of bone marrow exposure GLP	Dimethachlor (CGA17020) technical Batch: 1710 Purity: 98.3% w/w Not confirmed if representative of the proposed technical specification. Vehicle: polyethylene glycol 400 (PEG 400).	NMRI mice. Single doses of 60, 180, and 600 mg/kg were administered to groups of 6 males and 6 females. 5 males and 5 females per test group were analysed for occurrence of micronuclei in PCEs. Negative control and high dose groups were sacrificed after 24, 48, and 72 hours; low and intermediate dose and positive control groups sacrificed	Negative, no significant increase in the incidence of micronucleated PCE was noted at any of the doses or time points. Two males dosed with 600 mg/kg bw died. Positive controls included.	[redacted] (1991)

Method, guideline, deviation if any	Test substance	Relevant information about the study (as applicable)	Observations/Results	Reference
		after 24 hours. In preliminary experiment maximum tolerated dose was established at 600 mg/kg bw.		
Micronucleus assay in bone marrow cells OECD 474 no deviations GLP	Dimethachlor (CGA17020) technical Batch: OP. 11000 Purity: 96.8 %.Vehicle: polyethylene glycol 400 (PEG 400).	Crl: CD1 mice. Single doses of 200, 400, 800 mg/kg/day males 500, 1000, 2000 mg/kg/day females	Negative, no increased incidence of micronuclei. Batch tested representative of new technical specification.	[redacted] (2020)

Table 43: Summary table of human data relevant for genotoxicity / germ cell mutagenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

2.6.4.1 Short summary and overall relevance of the provided information on genotoxicity / germ cell mutagenicity

Eight genotoxicity tests have been conducted on dimethachlor. Six were *in vitro* studies investigating gene mutation in bacteria and mammalian cells, the effects on chromosomes (clastogenicity and aneugenicity), and on DNA (unscheduled DNA synthesis).

The *in vitro* micronucleus assay (Naumann, 2019) was conducted with a dimethachlor batch, which was spiked with specific impurities, up to the limit of specification. For impurities with no additional or different QSAR alerts compared to parent, testing on a spiked batch can be considered to address equivalence. Since the results of this assay were positive though, further studies to clarify if the effect is due to the parent and to identify safe levels for the impurities were deemed necessary. Therefore, the Applicant conducted *in vitro* (and in some cases also *in vivo*) genotoxicity studies on the single, isolated impurities of the spiked batch (see confidential Volume 4 or Confidential Annex to CLH report), and a new *in vivo* micronucleus assay with dimethachlor technical on a non-spiked, representative batch of technical material ([redacted], 2020). An *in vivo* follow up with the spiked batch, could raise questions with regard to the hazard and also proof of exposure of each single impurity. Therefore, testing of pure, isolated impurities was decided in order to have a clear picture for the impurities (since testing is performed at higher concentrations than the specification), and also to clarify the properties of the parent. The *in vivo* micronucleus study ([redacted], 1991) did not show increased incidence of micronuclei. Although the *in vivo* assay was negative, there were several deficiencies identified during dimethachlor evaluation [dimethachlor DAR (DAR Vol 3 B6, 2007)]. Based on the results of the new *in vivo* assay ([redacted], 2020), dimethachlor technical (batch representative of proposed technical specification) tested negative for genotoxicity as there was no evidence of clastogenic or aneugenic effects.

All tested impurities were also shown to be negative in the *in vitro/in vivo* genotoxicity assays conducted (Volume 4).

There is no evidence of a mutagenic effect of dimethachlor in *in vitro* studies or in *in vivo* studies on somatic cells therefore, no *in vivo* studies in germ cells were warranted.

2.6.4.2 Comparison with the CLP criteria regarding genotoxicity / germ cell mutagenicity

Overall, there is no evidence that dimethachlor is genotoxic when assessed in a range of *in vitro* and *in vivo* assays. There is no evidence that there is any risk of genotoxic effects in humans exposed to dimethachlor.

2.6.4.3 Conclusion on classification and labelling for genotoxicity / germ cell mutagenicity

No classification. No change to the existing decision on classification (i.e. no classification) is proposed.

2.6.5 Summary of long-term toxicity and carcinogenicity [equivalent to section 10.9 of the CLH report template]

Table 44: Summary table of animal studies on long-term toxicity and carcinogenicity

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
Carcinogenicity Study OECD 453 (1981). GLP: Yes Rat: Tif:RAIf (SPF) 50/sex/group for carcinogenicity 10/sex/group for one year interim kill 10/sex/group for haematological, biochemical and urine analysis, 10/sex/group for haematological investigations	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: diet 0, 20, 300, 4000 ppm 0, 0.765, 11.1 and 157.3 mg/kg bw/day in males; 0, 0.892, 12.9, and 182.6 mg/kg bw/day in females For 24 months	**<u>Non-neoplastic findings</u>** **<u>4000 ppm (157.3 mg/kg bw/day in males, 182.6 mg/kg bw/day in females)</u>** ↑ *Survival*: 72% in both sexes after 104 weeks, controls 48% in males and 52% in females. ↓ *Body weight gain:* up to 11.6% in males (week 75) and 15.2% in females (week 103). ↓ *Food consumption*: males mainly during the first three months, females throughout the first year and sporadically for remainder of study. Cumulative for study 3.8% males, 8.0% females. *Haematology:* ↓ platelets in males max. 12% week 105, 14% in females; ↑ prothrombin time in males in first year of treatment maximum 29% week 13. *Blood biochemistry*: ↑ gamma-glutamyl transpeptidase activity males 14.5 times control week 52, 3 times control week 105. *Organ weights*: ↑ Relative liver 9.4% males week 105, 19.5% females week 53; ↑ Absolute kidney 8.1% males week 105, ↑ Relative kidney 22.2% males, 14.2% females week 105. *Histopathology*: Hepatocyte hypertrophy 24/60 males, 17/60 females (0/60 controls); Liver cytoplasmic inclusion bodies 27/60 males (0/60 controls). **<u>300 ppm (11.1 mg/kg bw/day in males, 12.9 mg/kg bw/day in females)</u>** No effects. **<u>20 ppm (0.765 mg/kg bw/day in males, 0.892 mg/kg bw/day in females)</u>** No effects. **<u>Neoplastic findings</u>** No overall increase in tumour incidence. Following extensive histopathological examination at 4 different levels of the respiratory epithelium of the **nasopharynx** a slightly increased incidence of **adenoma of the respiratory epithelium** in 3 high dose males (3/60; control group: 0/60) was observed. **NOAEL for chronic toxicity:** 300 ppm (11.1 or 12.9 mg/kg body weight per day for males and females, respectively)	[redacted] & [redacted] (1995)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
		LOAEL for chronic toxicity: 4000 ppm (157.3 mg/kg bw/day in males, 182.6 mg/kg bw/day in females) **NOAEL for carcinogenicity:** 300 ppm (11.1 or 12.9 mg/kg body weight per day for males and females, respectively) **LOAEL for carcinogenicity**: 4000 ppm (157.3 mg/kg bw/day in males, 182.6 mg/kg bw/day in females) - target organs: liver (increased liver weight, cytoplasmatic inclusion bodies, hepatocyte hypertrophy, increased gamma-glutamyl transpeptidase activity), kidney (increased kidney weight), nasopharynx (adenoma).	
Carcinogenicity Study OECD 451 (1981). OECD 453 (1981). GLP Mouse: Tif: MAGf 50/sex/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: diet 0, 20, 300, 4000 ppm 0, 2.25, 32.3 and 488.1 mg/kg bw/day in males; 0, 2.17, 31.2, and 450.9 mg/kg bw/day in females For 18 months	**<u>Non-neoplastic findings</u>** **<u>4000 ppm (488.1 mg/kg bw/day in males, 450.9 mg/kg bw/day in females)</u>** ↓ *Body weight*: 9.7% and 10.0% in males and females respectively week 77. *Organ weights*: ↑ 17.1%, 12.2% liver to body weight ratios in males and females respectively, ↑ 41% and 20.9% kidney to body weight ratios in males and females respectively. *Histopathology*: hepatocyte hypertrophy 45/50 males (25/50 controls), 46/50 females (27/50 controls); incidence and severity of 25/50 males renal chronic progressive nephropathy (control 3/50), 16/50 males renal tubular dilatation (control 2/50), 33/50 renal cysts (control 16/50) and 27/50 female renal tubule atrophy (control 16/50). **<u>300 ppm (32.3 mg/kg bw/day in males, 31.2 mg/kg bw/day in females)</u>** *Organ weights*: ↑ 16.2% kidney to body weight ratios in males. **<u>20 ppm (2.25 mg/kg bw/day in males, 2.17 mg/kg bw/day in females)</u>** No effects. **NOAEL for chronic toxicity**: 300 ppm (32.3 mg/kg bw/day for males and 31.2 mg/kg bw/day in females). **LOAEL for chronic toxicity**: 4000 ppm (488.1 mg/kg bw/day in males, 450.9 mg/kg bw/day in females) **<u>Neoplastic findings</u>** The incidence of **hepatocellular tumours** was slightly increased in 4000 ppm males. The incidence of **benign hepatoma** was slightly increased in top dose males, but still well within the historical control range.	[redacted] (1995)

<table>
<tr><th>Method, guideline, deviations[1] if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results
- NOAEL/LOAEL
- target tissue/organ
- critical effects at the LOAEL</th><th>Reference</th></tr>
<tr><td></td><td></td><td>
The incidence of hepatocellular carcinoma was increased (non-significantly) in low and top dose males, with the values above historical control range at top dose. However, there was no dose-response.
[Historical control data are considered appropriate and relevant since they have been generated from studies conducted in the same laboratory within +/- 5 years (dimethachlor treatment in [redacted] study started in July 1992 and ended in January 1994, and the studies from which HCD originates were conducted in the time period February 1988 – November 1992), and in the same stain of mouse. They comprise the data from seven 18-month studies with 50-70 animals per study examined.]
<table>
<tr><th>MALES</th><th colspan="4">Dose of Dimethachlor (ppm)</th></tr>
<tr><th></th><th>0</th><th>20</th><th>300</th><th>4000</th></tr>
<tr><td>Examined</td><td>50</td><td>50</td><td>49</td><td>50</td></tr>
<tr><td>No. of animals with hepatoma
(% of examined)</td><td>12 (24)</td><td>13 (26)</td><td>5 (10)</td><td>17 (34)</td></tr>
<tr><td></td><td colspan="4">HC 24% (12-46%)</td></tr>
<tr><td>No. of animals with carcinoma
(% of examined)</td><td>4 (8)</td><td>12 (24)</td><td>7 (14)</td><td>12 (24)</td></tr>
<tr><td></td><td colspan="4">HC 11% (0-16%)</td></tr>
<tr><td>No. of animals with hepatoma or carcinoma
(% of examined)</td><td>15 (30)</td><td>18 (36)</td><td>8 (16)</td><td>23 (46)</td></tr>
<tr><td></td><td colspan="4">HC 32% (12-48%)</td></tr>
</table>
The incidence of pulmonary adenomas was slightly increased in 300 ppm males and in all treated female groups. However, no dose-response was observed for males, the values were well within the historical control (HC) range (or just slightly above in case of mid dose males) and below statistical significance.
The incidence of pulmonary carcinomas was slightly increased in top dose males, but with no clear dose-response and both control group and high dose group males showed incidences which were above the historical control range.

[Historical control data are considered appropriate and relevant since they have been generated from studies conducted in the same
</td><td></td></tr>
</table>

<table>
<tr><th>Method, guideline, deviations[1] if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results
- NOAEL/LOAEL
- target tissue/organ
- critical effects at the LOAEL</th><th>Reference</th></tr>
<tr><td></td><td></td><td>laboratory within +/- 5 years (dimethachlor treatment in [redacted] study started in July 1992 and ended in January 1994, and the studies from which HCD originates were conducted in the time period February 1988 – November 1992), and in the same stain of mouse. They comprise the data from seven 18-month studies with 50-70 animals per study examined.]
<table>
<tr><th>MALES</th><th colspan="4">Dose of Dimethachlor (ppm)</th></tr>
<tr><td></td><td>0</td><td>20</td><td>300</td><td>4000</td></tr>
<tr><td>Examined</td><td>50</td><td>50</td><td>49</td><td>50</td></tr>
<tr><td>No. of animals with adenomas
(% of examined)</td><td>8
(16)</td><td>3
(6)</td><td>14
(29)</td><td>8
(16)</td></tr>
<tr><td></td><td colspan="4">HC 20% (8-28%)</td></tr>
<tr><td>No. of animals with carcinoma
(% of examined)</td><td>6
(12)</td><td>2
(4)</td><td>4
(8)</td><td>9
(18)</td></tr>
<tr><td></td><td colspan="4">HC 5% (2-9%)</td></tr>
<tr><td>No. of animals with adenomas or carcinomas
(% of examined)</td><td>13
(26)</td><td>5
(10)</td><td>16
(33)</td><td>15
(30)</td></tr>
<tr><td></td><td colspan="4">HC 25% (12-33%)</td></tr>
<tr><td>FEMALES</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Examined</td><td>50</td><td>50</td><td>50</td><td>50</td></tr>
<tr><td>No. of animals with adenoma
(% of examined)</td><td>0
(0)</td><td>2
(4)</td><td>3
(6)</td><td>4
(8)</td></tr>
<tr><td></td><td colspan="4">HC 6% (2-13%)</td></tr>
<tr><td>No. of animals with carcinoma
(% of examined)</td><td>3
(6)</td><td>1
(2)</td><td>1
(2)</td><td>1
(2)</td></tr>
<tr><td></td><td colspan="4">HC 4% (2-7%)</td></tr>
<tr><td>No. of animals with adenomas or carcinomas
(% of examined)</td><td>3
(6)</td><td>3
(6)</td><td>4
(8)</td><td>5
(10)</td></tr>
<tr><td></td><td colspan="4">HC 11% (5-18%)</td></tr>
</table>
NOAEL for carcinogenicity: 4000 ppm (488.1 mg/kg bw/day in males, 450.9 mg/kg bw/day in females).</td><td></td></tr>
</table>

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
		- target organ: kidney (increased incidence and severity of kidney changes (chronic progressive nephropathy, renal tubular dilatation and renal cysts in males, and renal tubular atrophy in females), liver (hepatocellular hypertrophy, increased relative liver weights, benign liver tumours in high dose males within the range of historical control data)	
Carcinogenicity Study OECD 451 (1981). GLP Mouse: albino (ICO:CD1 (Crl)) 50/sex/group for carcinogenicity 10/sex/group for 9 month interim kill 10/sex/group for haematology	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: diet 0, 20, 300, 1500, 4000 ppm 0, 2.54, 34.3, 184 and 511 mg/kg bw/day in males; 0, 2.25, 31.4, 162 and 454 mg/kg bw/day in females For 18 months	**Non-neoplastic findings** **4000 ppm (511 mg/kg bw/day in males, 454 mg/kg bw/day in females)** ↓ *Body weight*: 8.0% males week 78. ↓ *Body weight gain*: males 29.5% weeks 1-13, 25.2% weeks 1-78. ↓ *Food utilisation efficiency*: males 35.2% weeks 1-12. *Organ weights:* ↑ Relative kidney males 32.9% week 40, 43.8% week 79-81; ↑ Relative liver 19.7% males, 22.0% females week 79-81. *Histopathology:* perilobular hepatocyte hypertrophy 35/50 males, 46/50 females (0/50 controls); chronic nephropathy 15/50 males (0/50 controls). **1500 ppm (184 mg/kg bw/day in males, 162 mg/kg bw/day in females)** ↓ *Body weight*: 6.15% males week 78. ↓ *Body weight gain*: males 20.9% weeks 1-13, 20.4% weeks 1-78. ↓ *Food utilisation efficiency*: males 24.7% weeks 1-12. *Organ weights:* ↑ Relative kidney males 18.0% week 40, 25.6% week 79-81; ↑ Relative liver 13.5% males, 11.7% females week 79-81. *Histopathology:* perilobular hepatocyte hypertrophy 20/50 males, 38/50 females (0/50 controls); chronic nephropathy 7/50 males (0/50 controls).	[redacted] (2001)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
		<u>300 ppm (34.3 mg/kg bw/day in males, 31.4 mg/kg bw/day in females)</u> *Organ weights:* ↑ Relative kidney males 8.0% 79-81. *Histopathology:* kidney atrophy tubular 35/50 males (25/50 controls), 21/50 females (16/50 controls). **<u>20 ppm (2.54 mg/kg bw/day in males, 2.25 mg/kg bw/day in females)</u>** No effects. **NO(A)EL for chronic toxicity:** 20 ppm (2.54 mg/kg bw/day in males, 2.25 mg/kg bw/day in females) **LO(A)EL for chronic toxicity:** 300 ppm (34.3 mg/kg bw/day for males, 31.4 mg/kg bw/day for females) No increase in tumour incidence. **NOEL for carcinogenicity:** 4000 ppm (511 mg/kg bw/day in males, 454 mg/kg bw/day in females). - target organs: kidney (chronic progressive nephropathy in males and renal tubular atrophy in females, increased kidney weights in males and females), liver (hepatocellular hypertrophy and increased liver weights and/or ratios in male and female)	

Table 45: Summary table of human data on long-term toxicity and carcinogenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 46: Summary table of other studies relevant for long-term toxicity and carcinogenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

2.6.5.1 Short summary and overall relevance of the provided information on long-term toxicity and carcinogenicity

Long-term studies via the dietary route were performed in rats and mice.

Study type (Reference)	NO(A)EL	Classification according to Regulation (EC) No 1272/2008 as amended
Chronic toxicity and carcinogenicity study (& , 1995)*	300 ppm (11.1 mg/kg bw/day)	Carc. Cat 2
Carcinogenicity study in mice, dietary (, 1995)*	300 ppm (31.2 mg/kg bw/day)	None
Carcinogenicity study in mice, dietary (, 2001)*	20 ppm (2.25 mg/kg bw/day)	None

*Included in original EU review

Summary of long-term toxicity and carcinogenicity

There is one carcinogenicity study in the rat and two studies in the mouse. These are guideline studies conducted to the GLP.

Rat

Dietary administration of dimethachlor to the rat at dose levels of 0, 20, 300, and 4000 ppm for two years resulted in decreased body weight gain and food consumption at 4000 ppm.

The liver was identified as the main target organ as indicated by increased gamma-glutamyl transpeptidase activities in males at 4000 ppm, as well as by increased liver weights and morphologic changes of hepatocyte (cytoplasmatic inclusion bodies in males and hepatocyte hypertrophy in males and females).

Nasopharyngeal adenomas arising from nasal respiratory epithelium in male rats in this study appear to be treatment-related, and that their relevance for humans cannot be ruled out. These tumours were observed at the highest dose tested (4000 ppm) but dimethachlor was well tolerated by the rats at this dose level, without effect on survival or overt signs of toxicity. Toxicological relevance of increased incidence of pooled benign and pooled benign or malignant tumours is considered unclear. Since evidence on dimethachlor's carcinogenicity in animals is limited, and do not justify Category 1B (possible carcinogenic potential of dimethachlor was observed in only one species, in one study, and in one sex (males); evidence for treatment-related increase in tumour incidence is considered adequate only for one tumour type - nasopharingeal adenomas arising from nasal respiratory epithelium; toxicological relevance of increased incidence of pooled benign and pooled benign or malignant tumours is considered unclear; nasopharingeal adenomas are benign tumours, and they were observed at low incidence rate; dimethachlor is not shown to be genotoxic), **Carc Category 2** is proposed.

NOAEL of **300 ppm** (equivalent to 11.1 or 12.9 mg/kg body weight per day for males and females, respectively) is proposed for **chronic toxicity and carcinogenicity** in rats, based on the LOAEL of 4000 ppm (157 mg/kg bw/day in males and 183 mg/kg bw/day in females) at which liver toxicity and nasopharyngeal adenomas were observed (& , 1995).

Mouse

Two mouse carcinogenicity studies were conducted. In order to clarify potential treatment-related effects observed in the first mouse study a second study was performed in a different mice strain.

1st study. Dietary administration of dimethachlor to mice (Tif:MAGf) at dietary dose levels of 0, 20, 300, and 4000 ppm for 18 months resulted in decreased body weight gain at the top dose level. As indicated by increased organ weights as well as macro- and micropathological findings, the kidney and liver were identified as target organs.

The increase of liver tumours in top dose males, as well as the increased incidence of pulmonary carcinomas, are not considered indicative of carcinogenicity, since the changes were not dose-related and/or the incidences were within the historical control range.

The **NOAEL** of **300 ppm**, equivalent to a mean intake of 32.3 mg/kg bw/day for males and 31.2 mg/kg bw/day for females, is proposed for **chronic toxicity** in mice, based on the LOAEL of 4000 ppm (equivalent to a mean intake of 488 mg/kg bw/day for males and 451 mg/kg bw/day for females) at which a lower body weight and food utilisation, increased incidence and severity of kidney changes (chronic progressive nephropathy, renal tubular dilatation and renal cysts in males, and renal tubular atrophy in females), as well as hepatocellular hypertrophy and increased liver weights were observed (, 1995).

2nd study. In the repeat mouse study dimethachlor was administered to CD-1 mice at dietary concentrations of 0, 20, 300, 1500, and 4000 ppm for 18 months. Dimethachlor was well tolerated without effects on survival, appearance and behaviour, food and water consumption. Body weight development was dose-dependently impaired in males at dose levels ≥1500 ppm mainly during the first 3 months of the study. A marginal effect on body weight development

was observed in 4000 ppm females during the second half of the study. The kidney and liver were identified as target organs as evident from absolute and relative organ weight changes as well as histopathological findings (increased incidence/severity of chronic progressive nephropathy and tubular atrophy, perilobular hypertrophy of hepatocytes).

The **NO(A)EL** of **20 ppm**, equivalent to a mean intake of 2.54 mg/kg body weight in males and 2.25 mg/kg body weight in females, is proposed for **chronic toxicity** in mice, based on the LOAEL of 300 ppm (equivalent to a mean intake of 34.3 mg/kg bw/day for males and 31.4 mg/kg bw/day for females) at which a slight (statistically non-significant) increase in absolute and relative kidney weights and in grading of tubular atrophy was observed in male mice. Dimethachlor was not oncogenic to mice at dose levels up to 4000 ppm ([redacted], 2001).

***In vitro* metabolism of dimethachlor sulfoxide (CGA048088) in rat and human liver and nasal microsomes**

In order to further investigate human relevance of nasal adenomas observed in the study, the Applicant conducted new mechanistic study in which metabolism of dimethachlor metabolite (dimethachlor sulfoxide, CGA048088) in rat and human liver and nasal microsomes was investigated *in vitro*.

In a validated *in vitro* system, para-hydroxylation of acetochlor sulfoxide (CSCA144786) and dimethachlor sulfoxide (CGA048088) was observed in the rat nasal, rat liver (acetochlor sulfoxide only) and human liver microsomes *in vitro*. However, acetochlor sulfoxide (CSCA144786) and dimethachlor sulfoxide (CGA048088) para-hydroxylation was not observed in the human nasal microsomes. The absence of para-hydroxylation in the human nasal tissue indicates that humans will be completely isolated from the nasal hazard that sulfoxide derivatives pose to the rat (Knowles et al., 2020).

Discussion on carcinogencity

Rat study

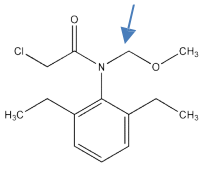
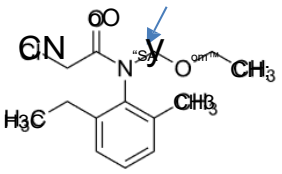
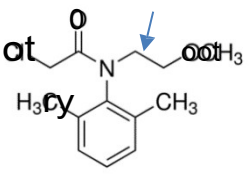
In the rat study ([redacted] & [redacted], 1995), the only treatment-related neoplastic change is considered to be the occurrence of nasopharyngeal adenoma in three males at 4000 ppm (157.3 mg/kg bw/day in males, 182.6 mg/kg bw/day in females).

The Applicant's assessment:

The Applicant considers that the occurrence of nasopharyngeal adenoma in three top-dose males (4000 ppm) is treatment-related. Nevertheless, due to differences in dimethachlor metabolism in rat and human nasal tissue (Knowles et al., 2020), the Applicant considers that this tumour type is not relevant for humans.

Dimethachlor, alachlor and acetochlor have a similar structure (Table 47). In the long-term studies, alachlor and acetochlor showed a high incidence of nasal tumours in male and female rats at 300/500/3000/5000 ppm (Table 47). In contrast, with dimethachlor there was a low incidence (3/60) restricted to males at top dose of 4000 ppm and the nasal adenoma were detected only after extensive examination of the muzzle.

Table 47: Overview of the chemical structures of chloroacetanilides and incidence of nasal tumours in male rats

	Alachlor	**Acetochlor**	**Dimethachlor**
Structure			
Dose	3000 ppm[a,b]	5000 ppm[a,c]	4000 ppm
Adenoma	65/103 (63%)	18/69 (26%)	3/60 (5%)
Carcinoma	7/103 (7%)	2/69 (2.9%)	0/60 (0%)

[a] nasal tumours also in females; [b] tumours observed down to 300 ppm; [c] tumours observed down to 500 ppm

The proposed mode of action for production of nasal tumours for alachlor and acetochlor in rats has been shown by Green *et al,* 2000[1] to be via two possible routes (Figure B.6.5.1-4).

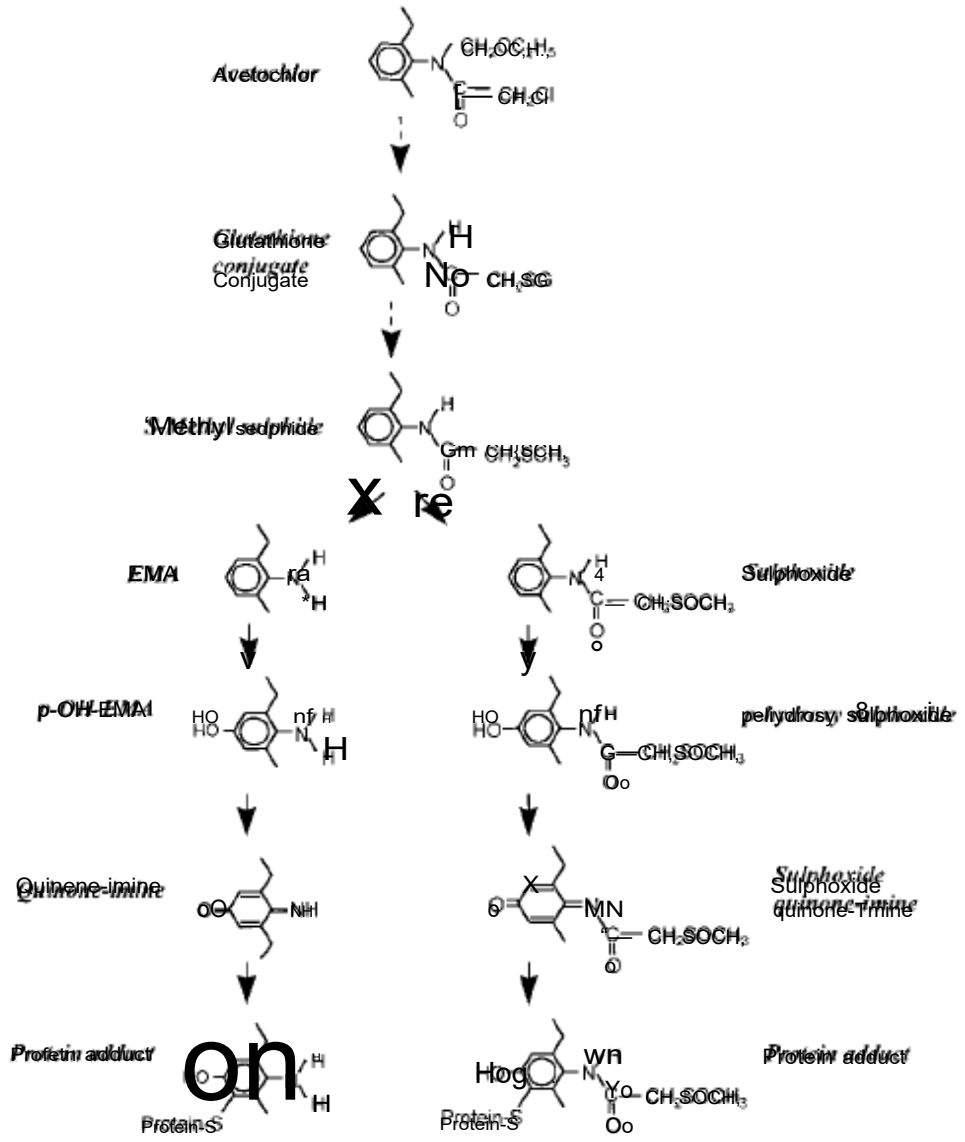


Figure 2.6.5-1: The metabolism of acetochlor to protein reactive quinone-imines in the rat

These are i) via the formation of aniline (EMA) and subsequent p-hydroxylation (scheme A) and ii) via the formation of sulphoxide and para-hydroxy sulphoxide (scheme B). Both pathways ultimately lead to a reactive quinone-imine and quinone-imine sulphoxide. Quinone-imines bind to tissue proteins and other nucleophiles such as glutathione.

The difference in the nature of the α-C atom of the N-alkyl group and its metabolic fate either oxidation to an aldehyde or an alcohol, markedly affects the susceptibility towards N-dealkylation between alachlor/acetochlor and dimethachlor (please see arrows in Table above). In dimethachlor, the alkyl group represents an alkylamine structure (level of oxidation = alcohol), whereas in alachlor and acetochlor this substituent represents an aminal structure (level of oxidation = aldehyde). Upon cleavage of the ether bridge in the alkyl group, alachlor (and acetochlor) will spontaneously form the corresponding anilines, whereas for dimethachlor stable alcohol derivatives are formed, which actually represent the major individual metabolites in rats.

[1] Green, T., Lee, R., Moore, R.B., Ashby, J., Willis, G.A., Lund, V.J. & Clapp, M.J.L. 2000. Acetochlor – induced rat nasal tumors: further studies on the mode of action and relevance to humans. Regulatory Toxicology and Pharmacology 32, 127-133 (KCA 5.5/01, NA_15089)

The sulphoxide was the major **acetochlor** plasma metabolite in the rat. In a separate 52 week study the sulphoxide metabolite caused hyperplasia and adenoma in the nasal cavities of rats and can be associated with the mode of action of formation of nasal tumours (ECHA, 2014[2]).

In the rat, the major metabolic reactions of **dimethachlor** included dealkylation leading to O-desmethyl derivatives, substitution of the chlorine by glutathione and oxidation of the methyl-phenyl group resulting in hydroxy-methyl derivatives. The primary alcohol formed by O-dealkylation was partially oxidised to the corresponding carboxylic acid or conjugated with glucuronic acid. Conjugation with glutathione was followed by degradation of the glutathione moiety resulting in various S-containing metabolites (i.e. cysteinates, mercapturates, sulphides, sulfoxides and sulfones). Minor metabolic pathways were the reduction of the methylene chloride moiety (-CH2Cl) giving rise to acetyl derivatives, the replacement of the chlorine by -OH and the subsequent oxidation to oxalic acid derivatives and the N-dealkylation to a secondary amide. N-dealkylation to a secondary amide was of minor importance; <1% of the administered dose was transformed to a secondary amide. This contrasts with alachlor/acetochlor, where N dealkylation is a major metabolic pathway (Figure B.6.5.1-4).

With dimethachlor neither free aniline derivatives nor the sulphate ester of the p-hydroxylated aniline were detected. This contrasts with alachlor/acetochlor, where the sulphoxide was the major acetochlor plasma metabolite in the rat.

To investigate this further for dimethachlor, and supplement the original biotransformation study in rat, a new biotransformation study ([redacted] & [redacted], 2018, CGA17020/0419) was conducted. With dimethachlor neither acetyl cysteine conjugate, methyl sulphide (ASMS), sulfoxide (ASMSO), dimethyl aniline (DMA), hydroxy methyl sulphide (OH-ASMS), chloro-dimethyl-phenylacetamide (CDMPA), nor hydroxy sulphoxide (OH-ASMSO) were detected in plasma or excreta.

In conclusion, there is no indication that dimethachlor is metabolised by N-demethylation to the aniline. However, dimethachlor does form very low amounts of sulphoxide metabolites with further hydroxylation. In a new mechanistic study (Knowles et al., 2020) conducted by the Applicant, evidence of acetochlor sulfoxide and dimethachlor sulfoxide para-hydroxylation, was observed in the rat nasal, rat liver (acetochlor sulfoxide only) and human liver microsomes *in vitro*. However, acetochlor sulfoxide and dimethachlor sulfoxide para-hydroxylation was not observed in the human nasal microsomes. The absence of the para-hydroxylation in the human nasal tissue indicates that humans will be completely isolated from the nasal hazard posed by sulfoxide derivatives.

The acetochlor review by ECHA (2014) concluded that the metabolism via scheme A in Figure B.6.5.1-4 leading to free aniline could contribute to the formation of quinone-imines (Coleman et al , 2000) and might occur in humans. However, as neither methyl sulphide (ASMS), dimethyl aniline (DMA), nor chloro-dimethyl-phenylacetamide (CDMPA) was formed from dimethachlor in the rat *in vivo* ([redacted] & [redacted], 2018; CGA17020/0419), this pathway can be ruled out for dimethachlor.

The Applicant considers that for dimethachlor other potential modes of action can also be excluded. Genotoxicity testing did not reveal any indication for a genotoxic potential by dimethachlor or its metabolites. There is no indication of cytotoxicity in the nasal cavities in the chronic rat study.

The Applicant, therefore, concludes that the postulated mode of action of the low incidence of nasal tumours by dimethachlor includes formation of very low amounts of sulphoxide metabolites with further hydroxylation. As 1) the Scheme B mode of action ("sulphoxide pathway") is not relevant for humans, due to qualitative differences in para-hydroxylation of the sulphoxide between rat, monkey and humans; 2) the scheme A metabolic pathway ("EMA pathway") is not evident in rats; and 3) other potential modes of action, such genotoxicity or cytotoxicity, can also be excluded, it is concluded that the nasal adenomas found in 3 male rats with dimethachlor are not of relevance for humans.

The Applicant also points out that:

- in contrast to typical rat carcinogenicity studies the muzzle (nasopharynx) was subject to extensive examination and no historical control data are available;
- the finding was restricted to 3 animals of one sex of the top dose of 4000 ppm only;
- the lesions were not apparent macroscopically, and they had no malignant features;
- genotoxicity testing did not reveal indication for a genotoxic potential by dimethachlor or its metabolites;
- there was no indication of cytotoxicity in the nasal cavities in the chronic rat study.

[2] Committee for Risk Assessment. Annex 1. Background document to the Opinion proposing harmonised classification and labelling at Community level of Acetochlor (ISO), 2014.

Regarding other neoplastic findings in the study, the Applicant is of the opinion that they naturally occur in the colony of rats used in the study, and that their incidences, distribution and morphologic appearance do not indicate a toxicologically relevant effect.

Therefore, no classification for carcinogenicity is required for dimethachlor, according to the Applicant.

The RMS's assessment:

The RMS is, however, of the opinion that there are indications of dimethachlor carcinogenicity in the present study, although the uncertainties are substantial.

Before the analysis of the specific neoplastic findings, the RMS points out several general issues that complicate the interpretation of histopathological findings in this study:

1. At the top dose (4000 ppm), at which an increase in tumours incidence was observed in male rats, survival of the animals was significantly higher compared to the control and lower dose groups (1.5 times increased survival in top dose group *versus* controls). It is well known that if the treatment increases survival, the test may overestimate the carcinogenic effects since the risk of getting a tumour increases with age (OECD 2012)[3].
2. In order to adjust for observed difference in survival rates, survival-adjusted analysis of tumour rates (Peto et al. 1980) was performed for the pools of a) benign, b) primary malignant, c) benign or primary malignant, and d) metastatic tumours. The analysis was not performed for individual tumour types, for which increased incidence was observed in males (these tumours were observed at low incidence rates, up to 4/60 in top dose group, and the approximation in Peto analysis may be unreliable if the number of tumours in a group is small; OECD 2012).
3. It is known that the carcinogenicity study design has low power, and is only able consistently to detect large increases over the negative control incidence (OECD 2012).
4. In contrast to top dose and control group, only limited number of tissue samples was examined in animals in the low and intermediate dose carcinogenicity sub-groups (lung, liver, kidney, testis, epididymis, muzzle, and all gross lesions). This approach can create problems in the statistical analysis of dose-response trends and cannot be recommended if dose-response characterization is an objective of a study (OECD 2012). Namely, the actual number of tumours in low and mid-dose groups may be higher than the observed values. For this reason, the study authors considered that the negative result of group comparison (i.e. top dose *versus* control) is considered more relevant for evaluation of this study than the trend test. This approach, however, has lower power than trend analysis (Haseman 1984)[4].
5. The extent of examination of the nasal cavity in chronic rodent studies was limited, so there are no adequate historical control data for this tumour type in the strain of rats used in the study (Tif:RAIf).

Pooled tumours analysis

An overall statistical analysis[5] of benign, primary malignant, benign or primary malignant, and metastatic tumours indicated a slightly increased incidence of male rats with benign, and with benign or malignant tumours at 4000 ppm. These increases were significant by trend analysis based on the nominal dose-level scores (i.e. 0, 20, 300, and 4000 ppm), while neither group comparison (control *versus* high dose) nor trend analysis based on the ordinal group-number scores (i.e. group 1, 2, 3, and 4) yielded significant results. The RMS agrees with the Applicant that this difference in results with respect to the way of calculation is probably due to the large numerical difference in dose levels between mid and high dose level. Also, the RMS agrees that due to the issue with the study design described in point 4) above, a pairwise comparison (which was non-significant for pooled tumours analysis in males) could be more appropriate than a trend test. Nevertheless, as stated above, this approach has lower power than trend analysis. The RMS, therefore, concludes that the relevance of observed increased incidence of pooled benign and pooled benign or malignant tumours is unclear.

Individual tumours analysis

[3] Organisation for Economic Co-operation and Development. Guidance document No. 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452 and 453. 2nd edition. Series on Testing and Assessment No. 162. ENV/JM/MONO(2011)47.

[4] Haseman JK. Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ Health Perspect. 1984;58:385-392.

[5] Calculated for "incidental" tumour scenario (Peto et al. 1980).

In males at the highest dose, i.e. 4000 ppm, following tumours were observed at increased incidence compared to control animals, and they were above historical reference range:

- benign tumours: granular cell tumour of cerebral meninges, mammary gland fibroadenoma, nasal adenoma, renal lipoma;
- malignant tumours: adrenocortical carcinoma, pancreatic islet carcinoma.

Since survival-adjusted Peto analysis was not performed by the study authors for individual tumour types, the RMS performed Poly-k (i.e. Poly-3) survival-adjustment, followed by Cochran-Armitage test for trend or Fisher's exact test for pairwise comparison (top dose group *versus* control) for each individual tumour type[6]. Only nasopharyngeal adenoma showed statistically significant increase in the trend test[7], both with the nominal dose-level scores (Chi2 for trend = 7.512, p = 0.0061, slope = 1.6e-05) and with the ordinal group-number scores (Chi2 for trend = 4.880, p= 0.0272, slope = 0.020). However, it should be pointed out that all these tumours had low incidences even at the top dose, so the power of statistical analysis is small. The toxicological relevance of non-nasal finding, therefore, remains unclear.

In top dose females, no treatment-related increase in tumour incidence was found, and the general analysis of microscopically observed neoplastic lesions indicated a decrease in the incidence of animals bearing benign tumours.

Nasopharyngeal adenomas

Following extensive histopathological examination at different levels of the respiratory epithelium of the nasopharynx, a slightly increased incidence of adenoma in 3 high dose males was observed (5% compared to 0% in controls). According to the study report, "**these tumours were obviously formed by respiratory epithelium**, as some of the neoplastic cells exhibited cilia and the tumors were located in the portion of nasal cavity known to be equipped with respiratory epithelium".

No such tumours occurred at lower doses in males or at any dose level in females.

In the previous assessment at the EU level (DAR, 2007), the RMS did not consider these tumours toxicologically relevant, based on evaluation of the toxicological significance of these tumours in context with the occurrence of nasal tumours in long term studies with other chloroacetanilides (i.e. alachlor and acetochlor) and mechanistic considerations, provided in an addendum to the DAR. On the other hand, a majority of the experts during the peer review process concluded that these tumours were of concern and consequently a classification of dimethachlor as Xn; R40 "Harmful; Limited evidence of a carcinogenic effect" was proposed (Conclusion regarding the peer review of the pesticide risk assessment of the active substance dimethachlor, Issued on 17 September 2008).

Comparison of dimethachlor and other chloroacetanilides and MoA relevance for humans

The RMS points out that the discussion by the Applicant presented above primarily relates to olfactory epithelial hyperplasia and neoplasia, while nasal adenomas in this study originated from respiratory nasal epithelia, according to the pathology report. Namely, acetochlor sulfoxide is rapidly hydroxylated in rat and mouse olfactory microsomal fractions, but not respiratory or liver fractions (Green, 1998b, in ECHA, 2014). In rats, the rate of hydroxylation of acetochlor sulphoxide to p-hydroxy acetochlor sulphoxide (precursor of quinoneimine) in olfactory microsomes occurs at a 6-fold higher rate than in respiratory microsomes (ECHA, 2014). Also, cell proliferation in rat nasal turbinate olfactory epithelium was significantly increased at 1750 and 5000 ppm acetochlor (1.3- to 1.5-fold and 1.5- to 2-fold, respectively), but not in respiratory epithelium (Hotz and Wilson, 1996a, in ECHA, 2014). Indeed, in the studies with acetochlor, alachlor and butachlor, which produced tumours of the nasal olfactory epithelium in rats (ECHA, 2014), the incidence of nasal respiratory epithelial hyperplasia was markedly lower than the incidence of olfactory epithelial hyperplasia (e.g., Table 48).

[6] OECD Series on Testing and Assessment. Guidance Document 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452 and 453, 2nd edition. ENV/JM/MONO(2011)47.
Patrick Royston, 2014. "PTREND: Stata module for trend analysis for proportions," Statistical Software Components S426101, Boston College Department of Economics.

[7] Trend test is considered justified, since the nasal tissues from all groups were analysed.

Table 48: Incidence of nasal proliferative lesions in F0 and F1 adults in 2-generation reproductive toxicity study with acetochlor (Milburn, 2001) (from ECHA, 2014)

	Findings	Dietary concentration of acetochlor (ppm)							
		Males				Females			
		0	200	600	1750	0	200	600	1750
F0	# tissues examined	26	26	26	26	26	26	26	26
	Olfactory epithelial Hyperplasia	0	0	0	3 12%	0	0	0	7** 27%
	Respiratory epithelial Hyperplasia	0	0	0	2 8%	0	0	0	2 8%
	Papillary adenoma	0*	0	0	4 15%	0	0	0	6* 21%
F1	# tissues examined	26	26	26	26	26	26	26	26
	Olfactory epithelial Hyperplasia	0*	0	0	7** 27%	0	0	4* 15%	14** 54%
	Respiratory epithelial Hyperplasia	0	0	0	1 4%	0	0	0	0
	Papillary adenoma	0	0	3 12%	9** 31%	0*	0	1 4%	17** 65%

* $p \leq 0.05$, Fisher's exact test
** $p \leq 0.01$, Fisher's exact test
† $p \leq 0.05$, Peto trend test
†† $p \leq 0.01$, Peto trend test

If "sulfoxide pathway" was responsible for nasal adenomas observed in the present carcinogenicity study with dimethachlor (EMA metabolic pathway is not evident in rats), olfactory, and not respiratory, nasal tumours or hyperplasia could be expected in rats.

Therefore, the question arises are some other mechanisms responsible for nasal adenoma occurrence in this study. Although genotoxicity and cytotoxicity are not expected to play a role, other potential mechanisms cannot be ruled out, as well as their possible relevance to humans. For example, although dimethachlor and its metabolites did not covalently bind to DNA *in vivo*, extensive binding to chromatin protein was observed, which may indicate the potential for interference with regulatory processes in DNA replication or transcription (Investigation for the potential for DNA binding of CGA17020 (Dimethachlor), Sageldorff et al., 1992).

The RMS, therefore, considers that nasopharyngeal adenomas arising from nasal respiratory epithelium in male rats in this study appear to be treatment-related, and that their relevance for humans cannot be ruled out. These tumours were observed at the highest dose tested (4000 ppm, equivalent to 157 mg/kg bw/day in males and 183 mg/kg bw/day in females), but dimethachlor was well tolerated by the rats at this dose level, without effect on survival or overt signs of toxicity.

Increased incidence of other tumours observed in the study is of unclear toxicological relevance.

Mice studies

In **Tif:MAGf mice** ([redacted] , 1995), a marked variability in the distribution of benign and malignant liver tumours was observed in male mice, including both control and treated animals. The number of animals with benign hepatoma was slightly increased in top dose males, although still well within the historical control range. Incidence of hepatocellular carcinoma was increased (non-significantly) in low and top dose males, with the values above historical control range at the top dose. Nevertheless, there was no dose-response. The incidence of a common pool of benign hepatoma and hepatocellular carcinoma was increased in top dose males. This increase was statistically significant ($p = 0.013$) but still within the range of historical control values, although near the maximum value. Furthermore, this p-value is slightly above the significance level of 0.01, which has been recommended as relevant for findings with the high spontaneous occurrence,[8] such are the observed liver tumours in mice.[9] Multiplicity of neoplastic hepatocellular lesions was not significantly increased ($p = 0.092$). In treated female animals, the incidence of hepatocellular neoplasia was very low and not indicative of a treatment-related effect.

[8] Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Peo J, Richards S, Wahrendorf J. Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments, in: Long-term and short-term screening assays for carcinogens: a critical appraisal, IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Supplement 2, Lyon 1980, 311-426.

[9] According to the literature, mouse strain used in this study (Tif:MAGf) has a high spontaneous rate of benign and malignant liver tumours, with higher incidences in males than in females (Carmichael NG, Enzmann H, Pate I, Waechter F. The significance of mouse liver tumor formation for carcinogenic risk assessment: results and conclusions from a survey of ten years of testing by the agrochemical industry. Environ Health Perspect. 1997;105(11):1196-203.).

The incidence of pulmonary adenomas was slightly increased in mid dose males and appeared to be increased in all treated female groups. However, no dose-response was observed for males, the values were well within the historical control range (or just slightly above in case of mid dose males) and below statistical significance. The incidence of pulmonary carcinomas was slightly increased in top dose males, attaining a level of statistical significance with a p-value of 0.026. Again, no clear dose-response was observed, and both the control group and the high dose group males showed incidences of pulmonary carcinoma which were above the historical control range. As discussed for hepatocellular tumours, the high spontaneous occurrence of pulmonary tumours justifies considering only p-values of less than 0.01 as biologically significant. The incidence as well as the multiplicity of benign and malignant pulmonary tumours combined revealed no significant dose-related increase, and the incidence of all pulmonary neoplasias was within the historical control range.
The RMS considers that the data on hepatocellular tumours incidence in top dose males and pulmonary tumours in both sexes, do not indicate an oncogenic activity of dimethachlor. Namely, these tumours are common spontaneous tumours in Tif:MAGf mice (Carmichael et al. 1997; Suter et al. 1979)[10] with a highly variable incidence, which complicates the evaluation of carcinogenicity studies. There was a lack of clear dose-response, the values were mostly within the relevant historical control range, and there was no increase in multiplicity of neoplastic lesions. Regarding lung tumours, pre-neoplastic lung lesions were not observed in the study, and 28-day and 90-day studies did not identify lung as a target organ in mice or other tested species.

In **ICO:CD1 (Crl) mice** ([redacted], 2001) no treatment-related neoplastic findings were observed, either on interim or terminal sacrifice.

The RMS considers that lack of carcinogenic findings in mice does not necessarily diminish the significance of increased incidence of nasopharingeal adenomas observed in rats. Namely, acetochlor also did not cause increased nasal olfactory or respiratory epithelial cell proliferation in mice (ECHA, 2018). It should be also noted that nasal cavity was histologically examined only in one mouse study ([redacted], 2001).

2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity

Based on the discussion above, classification for carcinogenicity Cat. 2 is proposed by the RMS.

Justification:

- Since there are no human data on dimethachlor carcinogenicity, Category 1A does not apply.
- Following aspects indicate that evidence in animals is limited, and do not justify Category 1B:
    - possible carcinogenic potential of dimethachlor was observed in only one species, in one study, and in one sex (males);
    - evidence for treatment-related increase in tumour incidence is considered adequate only for one tumour type (nasopharingeal adenomas arising from nasal respiratory epithelium); toxicological relevance of increased incidence of pooled benign and pooled benign or malignant tumours is considered unclear;
    - nasopharingeal adenomas are benign tumours, and they were observed at low incidence rate (3/60 male rats at the top dose);
    - dimethachlor is not shown to be genotoxic.
- Category 2 is, therefore, proposed, based on limited evidence of carcinogenicity in animal studies.

Table 49: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
Rat, Tif:RAIf	Nasopharyngeal adenoma,	No	No	No	Males	No	Oral, diet	MoA not known: relevance for

[10] Suter P, Luetkemeier H, Zakova N, Christen P, Sachsse K, Hess R. Lifespan studies on male and female mice and rats under SPF-laboratory conditions. Arch Toxicol Suppl. 1979;(2):403-7.

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
	not found in controls							humans cannot be ruled out
Mouse, ICO:CD1 (Crl)	None	n/a	n/a	n/a	n/a	n/a	Oral, diet	n/a
Mouse Tif: MAGf	liver and lung tumours: not dose-related and/or within historical control range	n/a	n/a	n/a	n/a	n/a	Oral, diet	n/a

2.6.5.3 Conclusion on classification and labelling for carcinogenicity

Based on limited evidence of carcinogenicity in animal studies, namely treatment-related increase in incidence of nasopharingeal adenomas arising from nasal respiratory epithelium in male rats, for which mode of action is not known and relevance for humans cannot be ruled out, classification for Carc Cat 2 (H351) is proposed by the RMS.

2.6.6 Summary of reproductive toxicity [equivalent to section 10.10 of the CLH report template]

Adverse effects on sexual function and fertility – generational studies [equivalent to section 10.10.1 of the CLH report template]

Table 50: Summary table of animal studies on adverse effects on sexual function and fertility – generational studies

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL	Reference
Reproductive toxicity Two generations / two F1 litters, one F2 litter OECD 416, 1983 - deviations from OECD 416, 2001: • No pre-mating estrous cycle monitoring in older guideline; • Attainment of sexual maturity	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 20, 300, 2000 and 4000 ppm Continuous in the diet 0, 20, 300, 2000, 4000 ppm (0, 1.33, 20, 133 and 267 mg/kg bw/day)	***Parental toxicity*** **<u>4000 ppm</u>:** **F0 (Pre-mating: 222-399 mg/kg bw/day males, 256-415 mg/kg bw/day females)** ↓ body weight gain (not significant) pre-mating (males 13% days 1-8, 9% days 1-99; females 14% days 1-8, 11% days 1-99); ↓ food consumption females (1st pre-mating 8% days 1-8, 1st gestation 5-9% not significant; 1st lactation from day 4 3-8% not significant; 2nd pre-mating 10% not significant; 2nd lactation max. 12% days 14-21 not significant). **F1 (Pre-mating: 237-443 mg/kg bw/day males, 285-463 mg/kg bw/day females)** ↓ body weight gain (not significant) pre-mating (males 11% days 1-99; females 10%	[redacted] (1994)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL	Reference
not assessed in F1 generation, nor ano-genital distance in F2 offspring if sex ratio perturbed or sexual maturity delayed in the F1 generation; • Only selected organ were weighed for the Parental, F1 or F2 generation (testes, epididymides and liver); • No primordial follicle quantification in the post lactational ovary of the F1 generation; • No sperm evaluation (caudal and testicular); • No histopathological examination of gross abnormalities from unselected F1 and F2 generation animals at weaning. GLP Rat, Sprague-Dawley Crl:CD (SD)BR strain 25/sex/group		days 1-99); ↓ food consumption females (pre-mating 8% days 1-99, gestation 15% days 0-7, lactation from day 4 8-12%). **<u>2000 ppm</u>:** **F0 (Pre-mating: 105-200 mg/kg bw/day males, 122-218 mg/kg bw/day females)** ↓ food consumption females (1st lactation days 14-21 14% not significant; 2nd lactation days 14-21 15%). **F1 (Pre-mating: 110-219 mg/kg bw/day males, 137-232 mg/kg bw/day females)** ↓ body weight gain pre-mating (males 13% days 1-99, not significant); ↓ *food consumption* females (pre-mating 6% days 1-99, gestation 13% days 0-7, lactation from day 4 5-7%, not significant). **<u>300 ppm</u>:** **F0 (Pre-mating: 15-32 mg/kg bw/day males, 18-33 mg/kg bw/day females)** No effects. **F1 (Pre-mating: 16-34 mg/kg bw/day males, 21-36 mg/kg bw/day females)** No effects. ***Reproduction toxicity*** **<u>4000 ppm</u>** No effects. ***Pup toxicity*** While livebirth index (number born alive/number born) ranged between 95 – 100%, viability index (number alive day 4 precull/number liveborn) ranged between 92 – 97%, and pups' viability between day 7 and day 4 postcull ranged from 91 – 96%, with no significant difference between groups in any of these indices, mortality markedly increased between day 7 – 14 in all groups, both treated and control. Weaning index (number alive at weaning/number alive at day 4 postcull) was 47% (91 surviving pup) in control group, 51% (89 surviving pups) in 20 ppm group, 56% (98 surviving pups) in 300 ppm group, 38% (58 surviving pups) in 2000 ppm group, and 43% (77 surviving pups) in 4000 ppm group. High mortality rate did not seem to be treatment related (there was no clear dose-response), and no plausible explanation was identified. Therefore, this was considered to be incidental and to reflect biological variability in the test species. In order to compensate for this study limitation, the study authors decided to perform a second mating of the P generation and to allow the rearing of the F1b offspring.	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL	Reference
		In F1b pups, appropriate viability indices were observed: livebirth index ranged from 92 – 100%, viability index from 89 – 99%, and weaning index from 85 – 99%. The indices were comparable between study groups. **<u>4000 ppm</u>** **F1 litters** ↓ body weight day 21 (systemic not lactation effect) (F1a males 13% not significant, females 12%; F1b males 14% males, 16% females). **F2 litters** ↓ body weight day 21 (systemic not lactation effect) (F2a males 19%, females 18%). **<u>2000 ppm</u>** **F1 litters** ↓ body weight day 21 (systemic not lactation effect) (F1a males 17%, females 4%, not significant; F1b males 11% males not significant, 11% females). **F2 litters** ↓ body weight day 21 (systemic not lactation effect) (F2a males 13%, females 11%). **<u>300 ppm</u>** No effects. **NOAEL:** Parental: 300 ppm (20 mg/kg/day) Reproduction/fertility: ≥4000 ppm (≥267 mg/kg/day) Offspring: 300 ppm (20 mg/kg/day) **LO(A)EL:** Parental: LOAEL of 2000 ppm (133 mg/kg bw/day) - critical effects: reduced body weight and food consumption Reproductive/fertility: LOEL of >4000 ppm (> 267 mg/kg bw/day) Offspring: LOAEL of 2000 ppm (133 mg/kg bw/day) - critical effects: reduced postnatal pup growth	

Table 51: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 52: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

2.6.6.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility – generational studies

Dimethachlor has been evaluated for adverse effects on sexual function and fertility in the rat in a two-generation reproduction toxicity study ([redacted], 1994). The study pre-dates the current OECD Test Guideline 416, 2001 and is therefore deficient in some endpoints including oestrus cyclicity, sperm motility and morphology, landmarks of sexual development and the pathology of the adults and pups (organ weight and histopathology) is limited. The deficiencies are considered not to compromise the outcome of the study given the clarity of the results obtained.

Clear parental toxicity (reductions in body weight and food consumption) was observed at the highest dose level of 4000 ppm; minimal effects only were observed at the intermediate dose level of 2000 ppm (LOAEL) and the NOAEL was 300 ppm (20 mg/kg/day). Despite the parental toxicity, there was no evidence for any effect of dimethachlor on sexual function and fertility in the rat at the highest dose level tested.

Systemic toxicity was also observed in the pups at 2000 ppm and 4000 ppm, with body weight decrements evident at weaning as a consequence of direct consumption of the diet (no body weight decrement was evident at birth or in the neonatal period). Based on this effect, NOAEL of 300 ppm (20 mg/kg/day) with LOAEL of 2000 ppm (133 mg/kg bw/day) are proposed for toxicity in offspring. No other toxicity was observed.

High mortality rates were observed in F1a pups (only 58 to 98 pups per group survived till weaning, with a weaning index of 38 – 56%). Since this could seriously impede the interpretation of the study results, the study authors decided to perform a second mating of the P generation and to allow the rearing of the F1b offspring. Since in F1b pups, appropriate viability indices were observed, and dimethachlor exerted similar effects in F1a and F1b pups at the same dose levels (body weight decrements at 2000 and 4000 ppm, as described above), the RMS considers that the study is acceptable for the evaluation of investigated reproductive toxicity parameters.

In summary, there were no adverse effects of dimethachlor on the sexual function and fertility of parental rats at dose levels that induced toxicity. Furthermore, there were no adverse effects of dimethachlor on the development of the offspring; body weight decrements at weaning were due to systemic toxicity. The reproductive NOEL was ≥4000 ppm (≥267 mg/kg/day).

2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility

In the classification system, reproductive toxicity is subdivided under two main headings:

(a) Adverse effects on sexual function and fertility

Any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

(b) Adverse effects on development of the offspring.

Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation.

There were no adverse effects on sexual function and fertility or on development of the offspring in the rat to warrant classification of dimethachlor as a potential human reproductive toxicant.

2.6.6.2 Adverse effects on development [equivalent to section 10.10.4 of the CLH report template]

Table 53: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ - critical effects at the LOAEL	Reference
Developmental toxicity OECD 414 1981; short dosing period cf. OECD 414, 2018 GLP Rat, Tif: RAI f strain 25 mated females/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 50, 350, 700 mg/kg bw/day by oral gavage on gestation days 6-15 Vehicle 0.5% CMC	***Maternal toxicity*** **700 mg/kg bw/day:** 5/25 deaths gestation days 9-14; 1/5 found dead day 9, 4/5 moribund having exhibited convulsions, dyspnea and/or hunched posture, piloerection; ↓ body weight gain (29%, days 6-11, 10% days 11-16; 17% days 6-16) , ↓ net weight change from day 6 [carcass weight (without gravid uterus weight) on day 21 minus day 6 body weight] (18%, although the difference was not statistically significant); ↓ food consumption (15% days 6-11, 9% days 11-16). **350 mg/kg bw/day:** ↓ food consumption (11% days 6-11; 6% days 11-16 not significant). **50 mg/kg bw/day:** No effects. ***Developmental toxicity*** **700 mg/kg bw/day:** ↑ skeletal anomalies: 53% litters cf. 25% controls due to ↑ wide fontanel (2% foetal & 16% litter incidence cf. 0% controls - HCD range 0-0.6% and 0-4.3% respec.); ↑ irregular ossification of occipital bone (2% foetal & 16% litter incidence cf. 0% controls - HCD range 0-0.9% and 0-6.3% respec.); ↑ bipartite occipital bone (1.5% foetal & 5% litter incidence cf. 0% controls – no HCD range reported); ↑ skeletal variations: reduced ossification or absence of phalangeal bones – foetal & litter incidences higher than HCD. **350 mg/kg bw/day:** ↑ skeletal anomalies: 50% litters cf. 25% controls due to ↑ wide fontanel (1% foetal & 4% litter incidence cf. 0% controls - HCD range 0-0.6% and 0-4.3% respec.); ↑ irregular ossification of occipital bone (1% foetal & 8% litter incidence cf. 0% controls - HCD range 0-0.9% and 0-6.3% respec.); ↑ skeletal variations: reduced ossification or absence of phalangeal bones – foetal & litter incidences higher than HCD. **50 mg/kg bw/day:** No effects.	[redacted] (1994)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ - critical effects at the LOAEL	Reference
		NOAEL: Maternal: 50 mg/kg/day Foetal: 50 mg/kg/day **LOAEL**: Maternal: 350 mg/kg/day - critical effects: reduced body weight and food consumption Foetal: 350 mg/kg/day - critical effects: developmental delay (increased incidence of poor or non-ossified bones) No evidence for teratogenicity.	
Developmental toxicity OECD 414 1981; short dosing period cf. OECD 414, 2018 GLP Rabbit, NZW strain 20 inseminated females/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 10, 100, 350, 600 mg/kg bw/day by oral gavage on gestation days 6-18 Vehicle 1.5% MC	***Maternal toxicity*** **600 mg/kg bw/day:** 3/3 deaths: 1/3 dead after one dose, 1/3 after two doses, 1/3 killed after two doses. No further animals allocated to group. **350 mg/kg bw/day:** 2/20 dead gestation days 18-20 (these mortalities were considered by the study authors to be incidental), 1/20 aborted day 22; ↓ body weight loss days 6-9 (-47%); ↓ body weight gain (35% days 6-19); ↓ food consumption (32% days 6-9, 18% days 9-12). **100 mg/kg bw/day:** No effects (1/20 animal was found dead on gestation day 18, but this mortality was considered to be incidental). ***Developmental toxicity*** **350 mg/kg bw/day:** No treatment-related effects. [↑ pre-implantation loss (43% cf. 23.5% controls) incidental to treatment but resulting in ↓ number live foetuses (5.5 cf. 8.4 controls) and ↓ litter weight (35%) due to fewer foetuses. Also, high incidence of malformation in all groups including control; no effect of treatment indicated.] **NOAEL**: Maternal: NOAEL of 100 mg/kg/day Foetal: NOEL of 350 mg/kg/day, NOAEL of >350 mg/kg bw/day **LOAEL**: Maternal: 350 mg/kg/day - critical effects: reduced body weight and food consumption	[redacted] (1993)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ - critical effects at the LOAEL	Reference
		Foetal: not determined No evidence for teratogenicity.	

Table 54: Summary table of human data on adverse effects on development

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 55: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

2.6.6.2.1 Short summary and overall relevance of the provided information on adverse effects on development

The prenatal developmental toxicity of dimethachlor was investigated in two guideline compliant studies, one in rats and one in rabbits. Both studies predate the current OECD Test Guideline 414 (2018) and the most notable deficiency is in the length of the dosing period. The current guideline requires dosing from implantation to termination whereas the previous version of the guideline required dosing over the period of major organogenesis only.

Administration of dimethachlor to pregnant rabbits at dose levels of 0, 10, 100, and 350 mg/kg bw/day during the period of organogenesis elicited slight maternal toxicity (e.g. body weight loss during the early treatment period, reduced mean body weight gain, reduced mean daily food consumption during the treatment period) at the top dose. Mortalities observed at 100 and 350 mg/kg bw/day were considered incidental. No effects on maternal reproductive parameters and no teratogenic or other embryotoxic effects were observed at any dose level. Based on the results of this study the **maternal NOAEL** was considered to be **100 mg/kg bw/day**, based on LOAEL of 350 mg/kg bw/day, at which reduced body weight and food consumption were observed in does. The **embryo/foetal NOEL** was determined to be **350 mg/kg bw/day** (the highest dose tested) ([redacted] 1993).

Pregnant rats were treated by oral gavage of dimethachlor at dose levels of 0, 50, 350, and 700 mg/kg bw/day during days 6 to 15 of pregnancy.

Maternal toxicity was indicated by mortality, decreased body weight gain and decreased food consumption at 700 mg/kg bw/day. In dams treated with 350 mg/kg bw/day, only slightly decreased food consumption was noted.
Incidence of total number of skeletal anomalies, and total number of skeletal variations that were above historical control (HC) range, was higher in mid-dose (350 mg/kg bw/day) and high-dose (700 mg/kg bw/day) foetuses and litters [HC data originate from the same strain and the same laboratory as the one where the study was performed, and comprise 17 studies (with 4559 – 8579 pups examined) from +/- 5 years period (January 1988 – September 1993)]. These changes represent poor or absent ossification and indicate developmental delay in affected pups.
The following skeletal variations/anomalies were considered treatment-related because the incidence of affected litters and/or foetuses was higher than the values of historical control groups:

- 700 mg/kg bw/day: absent ossification of metatarsal 1 and proximal phalanx of anterior and posterior digits; poor ossification of proximal phalanx of anterior and posterior digit; irregular ossification of occipital bone; wide fontanel; bipartite occipital bone;
- 350 mg/kg bw/day: poor ossification of proximal phalanx of anterior digit; absent and/or poor ossification of proximal phalanx of posterior digits; irregular ossification of occipital bone; wide fontanel.

The question is, however, are these changes secondary to maternal toxicity. While clear signs of maternal toxicity were observed in high-dose dams (mortality[11]; up to 29% decreased body weight gain and 18% decreased corrected mean maternal body weight change; decreased food consumption), maternal toxic effects of dimethachlor are unclear in mid-dose dams. In mid-dose dams, there were no mortality, clinical signs (haemorrhagic discharge in the perineal area or mouth seen for one or two days) were observed in only one animal, and body weight gain was not significantly decreased (by 5% compared to control, with no effect on corrected mean maternal body weight change). Only food consumption during dimethachlor treatment was statistically significantly decreased compared to controls during p.c. day 6-11 (by 11%), and non-significantly during p.c. day 11-16 (by 6%), but it could be also caused by the change in food palatability. As pointed out in the CLP Guidance, "in general it is very difficult to prove a causal relationship between a parentally mediated mechanism and adverse effects in the offspring" and "in order to determine whether a reproductive toxic effect is independent or secondary to a parental effect, it would be most appropriate to correlate individual data for offspring and their parents. Nevertheless, associations between parental and offspring effects do not by default prove a causal relationship." Regarding the nature of foetal changes, the CLP Regulation (Annex I: 3.7.2.4.3.) states that "classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity".
The RMS analysed whether increased incidence in a total number of skeletal anomalies and a total number of skeletal variations that were above the HC range was correlated to food intake during dimethachlor treatment period in mid-dose group, while being aware that a potential statistical correlation still does not necessarily mean a causal relationship. Mixed regression model [with animal food intake as dependent variable; presence of skeletal anomaly/skeletal variation above HC range, and time period (i.e. p.c. day 6-11 or p.c. day 11-16) as fixed effect variables; and animal id as random effect variable] showed that mid-dose animals with skeletal anomalies/variations above HC range had greater risk for lower food intake (-2.2 g; 95% confidence interval -4.4 to -0.1 g; p = 0.037) compared to mid-dose animals without skeletal anomalies/variations above HC range.

Although it is not clear whether maternal toxicity is present in mid-dose dams, the transient nature of observed changes (skeletal variations/anomalies in high- and mid-dose dams), and their correlation with reduced food intake in dams, lead the RMS to conclude that the evidence which would justify a classification for developmental toxicity is not strong enough in case of this study.

Dimethachlor was not teratogenic at dose levels up to 700 mg/kg bw/day. Based on the results of this study, the **maternal** and **embryo/foetal NOAEL** was determined to be **50 mg/kg bw/day in rats**, based on LOAEL of 350 mg/kg bw/day at which reduced body weight and food consumption were observed in dams and developmental delay (increased incidence of poor or non-ossified bones) was observed in pups ([redacted] 1994).

In summary, dimethachlor investigated in the pregnant rat and pregnant rabbit, induced maternal toxicity at high doses but did not produce adverse effects on foetal development.

2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development

In the classification system, adverse effects on development of the offspring include any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation.

Dimethachlor is currently not classified for reproductive toxicity under classification Regulation (EC) No 1272/2008. The animal studies demonstrate that dimethachlor does not cause effects on fertility in the rat, although with a caveat that several parameters were not evaluated (Table 50) since the two-generation study was performed in line with the older Guideline (TG OECD 416, 1983). In developmental toxicity studies in the rat and rabbit, no embryotoxic, foetotoxic or teratogenic effects of treatment were observed. Minor effects in developmental delay (delayed ossification) were seen only in the rat at ≥ 350 mg/kg bw/day, and were considered transient in nature, secondary to maternal toxicity (in high-dose dams) and correlated with decreased food intake. There are no human data for dimethachlor. Therefore, it was concluded that present data do not indicate a need to revise the classification for dimethachlor for reproductive toxicity.

2.6.6.3 Adverse effects on or via lactation [equivalent to section 10.10.7 of the CLH report template]

Table 56: Summary table of animal studies on effects on or via lactation

[11] In section 3.7.2.4.4. of the CLP Regulation it is stated that "maternal mortality greater than 10 % is considered excessive and the data for that dose level shall not normally be considered for further evaluation". In high-dose dams mortality was 20%.

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Reproductive toxicity Two generations / two F1 litters, one F2 litter OECD 416, 1983 (deviations from OECD 416, 2001) GLP Rat, Sprague-Dawley Crl:CD (SD)BR strain 25/sex/group	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 20, 300, 2000 and 4000 ppm Continuous in the diet	***Parental toxicity*** **<u>4000 ppm</u>:** **F0 (Pre-mating: 222-399 mg/kg bw/day males, 256-415 mg/kg bw/day females)** ↓ body weight gain (not significant) pre-mating (males 13% days 1-8, 9% days 1-99; females 14% days 1-8, 11% days 1-99); ↓ food consumption females (1st pre-mating 8% days 1-8, 1st gestation 5-9% not significant; 1st lactation from day 4 3-8% not significant; 2nd pre-mating 10% not significant; 2nd lactation max. 12% days 14-21 not significant). **F1 (Pre-mating: 237-443 mg/kg bw/day males, 285-463 mg/kg bw/day females)** ↓ body weight gain (not significant) pre-mating (males 11% days 1-99; females 10% days 1-99); ↓ food consumption females (pre-mating 8% days 1-99, gestation 15% days 0-7, lactation from day 4 8-12%). **<u>2000 ppm</u>:** **F0 (Pre-mating: 105-200 mg/kg bw/day males, 122-218 mg/kg bw/day females)** ↓ food consumption females (1st lactation days 14-21 14% not significant; 2nd lactation days 14-21 15%). **F1 (Pre-mating: 110-219 mg/kg bw/day males, 137-232 mg/kg bw/day females)** ↓ body weight gain pre-mating (males 13% days 1-99, not significant); ↓ *food consumption* females (pre-mating 6% days 1-99, gestation 13% days 0-7, lactation from day 4 5-7%, not significant). **<u>300 ppm</u>:** **F0 (Pre-mating: 15-32 mg/kg bw/day males, 18-33 mg/kg bw/day females)** No effects. **F1 (Pre-mating: 16-34 mg/kg bw/day males, 21-36 mg/kg bw/day females)** No effects. ***Reproduction toxicity*** **<u>4000 ppm</u>** No effects. ***Pup toxicity*** [Unusually high F1a pup loss between 7-14 for F1a litters in control and treated groups. A reason for this finding could not be detected so it was considered incidental and a reflection of the biological variability within this species] **<u>4000 ppm</u>** **F1 litters** ↓ body weight day 21 (systemic not lactation effect) (F1a males 13% not significant, females 12%; F1b males 14% males, 16% females). **F2 litters**	[redacted] (1994)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
		↓ body weight day 21 (systemic not lactation effect) (F2a males 19%, females 18%). **2000 ppm** **F1 litters** ↓ body weight day 21 (systemic not lactation effect) (F1a males 17%, females 4%, not significant; F1b males 11% males not significant, 11% females). **F2 litters** ↓ body weight day 21 (systemic not lactation effect) (F2a males 13%, females 11%). **300 ppm** No effects. **NOAEL:** Parental: 300 ppm (20 mg/kg/day) Reproduction/fertility: ≥4000 ppm (≥267 mg/kg/day) Offspring: 300 ppm (20 mg/kg/day) **LO(A)EL:** Parental: LOAEL of 2000 ppm (133 mg/kg bw/day) - critical effects: reduced body weight and food consumption Reproductive/fertility: LOEL of >4000 ppm (>267 mg/kg bw/day) Offspring: LOAEL of 2000 ppm (133 mg/kg bw/day) - critical effects: reduced postnatal pup growth	

Table 57: Summary table of human data on effects on or via lactation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 58: Summary table of other studies relevant for effects on or via lactation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

2.6.6.3.1 Short summary and overall relevance of the provided information on effects on or via lactation

The two-generation reproduction toxicity study of dimethachlor provided no evidence of impaired nursing behaviour or decreased pup viability during lactation; no direct, adverse effect on the offspring due to transfer of the chemical via the milk or to the quality of the milk was indicated. Namely, reduction in the postnatal pup growth (decrease in

body weight) manifested only after the first, and even more, after the second week postpartum, when it is expected that pups start to nibble their' mothers' food.

2.6.6.3.2 Comparison with the CLP criteria regarding effects on or via lactation

The classification is intended to indicate when a substance may cause harm due to its effects on or via lactation and is independent of consideration of the reproductive or developmental toxicity of the substance. There were no effects to warrant classification of dimethachlor for effects on or via lactation.

2.6.6.4 Conclusion on classification and labelling for reproductive toxicity

No classification. No change to the existing decision on classification (i.e. no classification) is proposed.

2.6.7 Summary of neurotoxicity

According to Commission regulation (EU) No 283/2013 neurotoxicity studies are required for active substances with structures that are similar or related to those capable of inducing neurotoxicity, and for active substances which induce specific indications of potential neurotoxicity, neurological signs or neuropathological lesions in toxicity studies at dose levels not associated with marked general toxicity. Dimethachlor belongs to the chemical class of chloroacetanilides. None of the chemicals of this class is suspected to act upon the nervous system in mammals.

Table 59: Summary table of animal studies on neurotoxicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results:** **- NOAEL/LOAEL** **- target tissue/organ** **-critical effect at LOAEL**	**Reference**
		The results of the toxicology studies performed with dimethachlor in different species after single application or after repeated treatment over different periods of time ranging from four weeks up to two years, did not reveal any neurotoxic effects. Therefore, no special neurotoxicity studies were performed.	

Regarding delayed polyneuropathy, according to Commission Regulation (EU) No 283/2013, these studies must be performed for active substances of similar or related structures to those capable of inducing delayed polyneuropathy such as organophosphorus compounds. Based on the pesticidal mode of action of dimethachlor and the lack of any specific neurotoxicity findings in the available studies, delayed neurotoxicity after acute and repeated exposure is not required to be tested for dimethachlor.

2.6.8 Summary of other toxicological studies

2.6.8.1 Toxicity studies of metabolites and impurities

Toxicity studies of groundwater metabolites

Toxicological studies were performed with the dimethachlor soil metabolites and groundwater metabolites CGA50266, CGA354742, CGA102935, CGA369873, CGA42443, CGA373464, SYN530561 and SYN547047.

Acute studies have been conducted on CGGA50266 and CGA354742, which showed that these metabolites are less toxic at comparable dose levels and to parent.

Genotoxicity studies performed in the original DAR (2007) showed no evidence of mutagenicity and clastogenicity for metabolites CGA354742, CGA369873, CGA373464, SYN530561, and CGA528702 (SYN547047 was incorrectly identified as SYN528702). In the current RAR genotoxicity studies have been performed for CGA50266, CGA354742, CGA369873, CGA373464, SYN530561, SYN547047, CGA102935 and CGA42443. There was no evidence of mutagenicity, anuegenicity or clastogenicity in any of these metabolites tested in any of the assays and therefore, all eight of the metabolites are considered to be non-genotoxic.

Short term studies were performed for CGA50266, CGA354742, CGA369873, CGA42443 and CGA373464. Effects seen with metabolites are different to parent, affecting the kidney, adrenal, thyroid, bone marrow and testis. In comparison to the parent dimethachlor (CGA17020) at comparable dose levels, the metabolites CGA50266, CGA354742 CGA369873, CGA42443 and CGA373464 are considered to be similarly or less toxic than parent dimethachlor. No repeat dose toxicity data is available for SYN530561, SYN547047 and CGA102935, however due to the similarity in chemical structure between these metabolites and other ground-water metabolites for which general toxicity data has been generated, the toxicity concerns for SYN530561, SYN547047 and CGA102935 are addressed using a read-across strategy.

Table 2.6.8.1-1 Overview of toxicity studies with groundwater metabolites of dimethachlor

Metabolite	**CGA 50266**	**CGA 354742**	**CGA 102935**	**CGA 369873**	**CGA 42443**	**CGA 373464**	**CGA 530561**	**SYN 547047**
Acute toxicity (LD50 mg/kg)								
rat, oral	> 2000	> 2000						
Genotoxicity								
Bacteria Reverse Mutation Assay (Ames)	negative	negative	negative	negative	negative	negative	negative	negative
In Vitro Mammalian Cell Gene Mutation Test	negative	negative	negative	negative	negative	negative	negative	negative
In Vitro Cytogenetic Test	negative	negative		negative				
In Vitro Chromosome aberration study			negative			negative	negative	negative
In Vitro Micronucleus	negative	negative	negative	negative	negative	negative	negative	negative
Repeated toxicity (NOAEL in mg/kg/d)								
28 day, rat				1261	72.7	480		
90 day, rat	400	69.6	71.7*				71.7*	71.7*

* read across to parent

Toxicity studies of dietary metabolites

Multi-QSAR assessment for genotoxicity has been conducted for all nine identified dietary metabolites.

CGA42443, SYN547047, CGA102935, CGA50266 and CGA35742 are also groundwater metabolites of dimethachlor and a full negative genotoxicity package is available (Table 2.6.8.1-1). Short-term studies have also been conducted for CGA42443, CGA102935, CGA50266 and CGA35742 (Table 2.6.8.1-1). For the remaining four dietary metabolites (CGA048086, CGA048090, CGA551032 and CGA39981), potential for genotoxicity has been addressed through a combination of QSAR, read-across and genotoxicity studies *in vitro*. For CGA048090 and CGA551032 negative Ames test (Chang, 2020) and *in vitro* micronucleus (Naumann, 2020) are available.

Three dietary metabolites (CGA50266, CGA354742 and CGA048090) were found above 0.01 mg/kg in field rotational crop trials. Repeat dose toxicity data is available for CGA50266 and CGA354742 (Table 67). No repeat-dose toxicity data is available for CGA048090 however concerns for general toxicity for this metabolite can be addressed through read-across to CGA354742, which has a 90 day study available ([redacted], 2002).

Therefore, all identified dietary metabolites of dimethachlor can be considered to be of no genotoxic concern based on either available in vitro/in vivo genotoxicity data or chemically supported read-across to similar molecules. The short-term studies show that CGA102935, CGA50266 and CGA35742 are no more toxic than parent.

2.6.8.2 Supplementary studies on the active substance

Potential for DNA binding

"1The potential for DNA binding of dimethachlor was investigated. Groups of two male Tif: RAIf (SPF) rats were pre-treated with 250 mg unlabelled dimethachlor or with vehicle for 2 weeks, and then given a single oral dose of 250 mg [^{14}C] dimethachlor/kg bw on day 15. After 24 hours the animals were sacrificed, liver DNA and chromatin protein were isolated and purified, and the specific radioactivity was determined. Dimethachlor or its metabolites did not covalently bind to DNA *in vivo*. However, extensive binding to chromatin protein may indicate a potential for interference with regulatory processes in DNA replication or transcription. The genotoxicity data generated on parent demonstrates that dimethachlor is not genotoxic.

Immunotoxic potential

A thorough review of the toxicology database for dimethachlor has shown no evidence of adverse effects on the immune system in rats, mice or dogs.

Studies with dimethachlor that were reviewed included short-term, subchronic and chronic studies in rats, mice and dogs, already described in RAR. Immune-related parameters were not investigated in developmental or generational tests in rats or rabbits.

The immune-related parameters that are most relevant and examined in detail in this review of the database were:

- Organ weights (spleen and thymus weights),
- Hematology parameters (white blood cell counts (WBC) and/or differential counts),
- Globulin levels in plasma,
- Micropathology findings in immune-related tissues such as spleen, thymus, lymph nodes, adrenals, bone marrow and Peyer's patches (GALT),
- Any increase in tumours in immune-related tissues,
- Evidence of enhanced infections in long-term studies that are compound-related,

Regarding searched literature and human data, there is no evidence from literature that dimethachlor may have the potential to be immunotoxic.

In addition, dimethachlor does not belong to a class of chemicals (e.g., the organotins, heavy metals, or halogenated aromatic hydrocarbons) that would be expected to be immunotoxic.

Endocrine disrupting properties

Please see section 2.10.

2.6.9 Summary of medical data and information

Information from manufacturing plant personnel, data collected on humans (public literature) and direct observations (information on adverse health incidences in public databases), information from epidemiology studies (public literature) indicate a low toxic potential of dimethachlor. Clinical signs after intentional ingestion were transient, non-specific and reversible (with symptomatic or even no treatment). Except of the irritating properties to eyes (and skin) and skin sensitization potential no marked systemic toxicity is expected. Standard first aid measures and symptomatic medical treatment are recommended after accidental or intentional exposure.

2.6.10 Toxicological end points for risk assessment (reference values)

Table 60: Overview of relevant studies for derivation of reference values for risk assessment

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Rat HanIBM:WIST (SPF)	25/26 day repeated dose dietary toxicity study	Dimethachlor (CGA17020) technical Batch: 1715 (identical with OP 110001) Purity: 96.8% w/w 0, 100, 700, 3000, and 5000 ppm 0, 9.5, 67, 294.8 and 487.9 mg/kg bw/day in males; 0, 10.0, 68.3, 304 and 485.2 mg/kg bw/day in females	Liver (clinical chemistry changes, increased weight, histopathology), - red blood cell parameters (lower MCHC, compensatory erythropoietic activity)	NOAEL: 700 ppm (67.0 mg/kg bw/day in males and 68.3 mg/kg bw/day in females)	LOAEL: 3000 ppm (294.8 mg/kg bw/day in males and 304.0 mg/kg bw/day in females)	[redacted] (1992a)
Rat: Tif: RAIf, (SPF)	28 day repeated dose oral (gavage) toxicity study	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 30, 150, and 750/350 mg/kg bw/day	Liver(clinical chemistry changes, increased weight, histopathology), red blood cell parameters (lower values of red blood cell parameters, tendency to macrocytosis, compensatory erythropoietic activity)	**NOEL:** 30 mg/kg bw/day.	**LOEL:** 150 mg/kg bw/day	[redacted](1993)
Mouse: HanIBM:NMRI (SPF)	28 day repeated dose dietary toxicity study	Dimethachlor (CGA17020) technical	Liver (increased weight, histopathology)	**NOEL:** 100 ppm (20.9 mg/kg bw/day in males and 23.2 mg/kg	**LOEL**: 1000 ppm (204.4 mg/kg bw/day in males and 232.3 mg/kg	[redacted] (1992b)

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
		Batch: 1715 (identical with OP 110001) Purity: 96.8% w/w 0, 100, 1000, 3000, and 7000 ppm 0, 20.9, 204.4, 623.7, and 1493.3 mg/kg bw/day in males; 0, 23.2, 232.3, 715.2 and 1783.7 mg/kg bw/day		bw/day in females)	bw/day in females)	
Dog: Beagle	28 day repeated dose dietary toxicity study Dose ranging study to no specific guidelines	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 500, 2000 and 4000 ppm 0, 15.28, 62.95 and 119.84 mg/kg bw/day in males; 0, 18.05, 70.24 and 118.59 mg/kg bw/day in females	Liver (ALP increase, increased weight, histopathology), thymus (lower weight, cortical atrophy)	**NO(A)EL**: 500 ppm (15.3 mg/kg bw/day in male and 18.1 mg/kg bw/day in females).	**LO(A)EL**: 2000 ppm (63.0 mg/kg bw/day in males and 70.24 mg/kg bw/day in females)	[redacted] (1993)
Rat: Tif: RAIf, (SPF)	90 day repeated dose dietary toxicity study	Dimethachlor (CGA17020) technical Batch: OP.	Liver (clinical chemistry, weight, histopathology)	**NOEL**: 30 ppm (2.21 mg/kg bw/day in males and females)	**LOEL**: 1000 ppm (71.7 mg/kg bw/day in males, 76.0 mg/kg bw/day in females)	[redacted] (1994)

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
		110001 Purity: 96.8% w/w 0, 30, 1000 and 6000 ppm 0, 2.21, 71.7 and 449.4 mg/kg bw/day in males; 0, 2.21, 76.0 and 457.4 mg/kg bw/day in females				
Mouse: Ico:CD1 (Crl)	90 day repeat dose dietary toxicity study	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8 % w/w 0, 100, 1000, 3500 and 7000 ppm 0, 17.5, 175, 614 and 1228 mg/kg bw/day in males; 0, 18.5, 185, 648 and 1296 mg/kg bw/day in females	liver ((increased weight, histopathology), kidney (increased weight, histopathology)	**NOEL**: 100 ppm (17.5 mg/kg bw/day in males and 18.5 mg/kg bw/day in females) **NOAEL**: 1000 ppm (175 mg/kg bw.day in males and 185 mg/kg bw/day in females)	**LOEL:** 1000 ppm (175 mg/kg bw.day in males and 185 mg/kg bw/day in females) **LOAEL**: 3500 ppm (614 mg/kg bw/day in males and 648 mg/kg bw/day in females)	[redacted] (1999)
Dog: Beagle	90 day repeat dose dietary toxicity study	Dimethachlor (CGA17020) technical Batch: P12 Krist 1.74 Purity: 93.8% w/w 0, 100, 350	Liver (clinical chemistry, weight, histopathology)	**NOEL**: 350 ppm (10.1 mg/kg bw/day in males and 10.4 mg/kg bw/day in females).	**LOEL:** 1250 ppm (35.4 mg/kg bw/day in males and 45.4 mg/kg bw/day in females)	[redacted] (1974)

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
		and 1250 ppm 0, 3.4, 10.1 and 35.4 mg/kg bw/day in males; 0, 3.1, 10.4, 45.4 mg/kg bw/day in females				
Dog: Beagle	90 day repeat dose dietary toxicity study	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 300, 1000 and 3000 ppm 0, 9.96, 32.28 and 104.3 mg/kg bw/day in males; 0, 10.81, 35.95 and 102.8 mg/kg bw/day in females	liver (clinical chemistry changes, increased weight, histopathology), red cell parameters	**NOAEL**: 300 ppm (9.96 mg/kg bw/day in males and 10.81 mg/kg bw/day in females)	**LOAEL:** 1000 ppm (equivalent to 32.28 mg/kg bw/day in males and 35.95 mg/kg bw/day in females)	[redacted] (1994)
Rat Tif: RAIf (SPF), hybrids of RII/1 x RII/2	28-day dermal toxicity study	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 10, 100, 1000 mg/kg bw/day	-	**NOAEL: >**1000 mg/kg bw/exposure		([redacted], 1993)
Rat: Tif:RAIf (SPF)	Carcinogenicity Study	Dimethachlor (CGA17020) technical	Liver (increased liver weight, cytoplasmatic inclusion bodies, hepatocyte	**NOAEL for carcinogenicity and chronic toxicity:** 300 ppm (11.1 or 12.9	**LOAEL**: 4000 ppm (157.3 mg/kg bw/day in males, 182.6	[redacted] & (1995)

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
		Batch: OP. 110001 Purity: 96.8% w/w Vehicle: diet 0, 20, 300, 4000 ppm 0, 0.765, 11.08 and 157.3 mg/kg bw/day in males; 0, 0.892, 12.90, and 182.6 mg/kg bw/day in females For 24 months	hypertrophy, increased gamma-glutamyl transpeptidase activity), kidney (increased kidney weight), nasopharynx (adenoma).	mg/kg body weight per day for males and females, respectively)	mg/kg bw/day in females)	
Mouse: Tif: MAGf	18 month feeding Study	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: diet 0, 20, 300, 4000 ppm 0, 2.25, 32.3 and 488.1 mg/kg bw/day in males; 0, 2.17, 31.2, and 450.9 mg/kg bw/day in females	Liver (increased liver weight, hepatocyte hypertrophy, liver tumours in high dose males within the range of historical control data), kidney (increased kidney weight, degenerative kidney lesions), lungs (carcinoma in high dose males, not dose related)	**NOAEL for chronic toxicity**: 300 ppm (32.3 or 31.2 mg/kg body weight per day for males and females, respectively) **NOAEL for carcinogenicity:** 4000 ppm (488.1 mg/kg bw/day in males, 450.9 mg/kg bw/day in females)	**LOAEL for chronic toxicity:** 4000 ppm (488.1 mg/kg bw/day in males, 450.9 mg/kg bw/day in females)	[redacted] (1995)

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Mouse: albino (ICO:CD1 (Crl))	18 month feeding Study,	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w Vehicle: diet 0, 20, 300, 1500, 4000 ppm 0, 2.54, 34.3, 184 and 511 mg/kg bw/day in males; 0, 2.25, 31.4, 162 and 454 mg/kg bw/day in females	Kidney (chronic progressive nephropathy in males and renal tubular atrophy in females, increased kidney weights in males and females), liver (hepatocellular hypertrophy and increased liver weights and/or ratios in male and female)	**NO(A)EL for chronic toxicity:** 20 ppm (2.54 mg/kg bw/day in males, 2.25 mg/kg bw/day in females) **NOEL for carcinogenicity:** 4000 ppm (511 mg/kg bw/day in males, 454 mg/kg bw/day in females)	**LO(A)EL for chronic toxicity:** 300 ppm (34.3 mg/kg bw/day for males, 31.4 mg/kg bw/day for females)	[redacted] (2001)
Rat, Sprague-Dawley Crl:CD (SD)BR strain	Multigeneration In rats, dietary/	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 20, 300, 2000 and 4000 ppm Continuous in the diet 0, 20, 300, 2000, 4000 ppm (0, 1.33, 20, 133 and 267 mg/kg bw/day)	Parental Reduced body weight and food consumption Reproductive/fertility No effects Offspring Reduced postnatal pup growth	**NOAEL:** Parental: 300 ppm (20 mg/kg/day) Reproduction/fertility: 4000 ppm (267 mg/kg/day) Offspring: 300 ppm (20 mg/kg/day)	**LOAEL**: Parental: 2000 ppm (133 mg/kg bw/day) Reproductive/fertility: >4000 ppm (> 267 mg/kg bw/day) Offspring: 2000 ppm (133 mg/kg bw/day)	[redacted], 1994)

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Rat, Tif: RAI f strain	Developmental toxicity (gavage)	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 50, 350, 700 mg/kg bw/day by oral gavage on gestation days 6-15 Vehicle 0.5% CMC	**Maternal** Decreased body weight gain and food consumption at ≥350 mg/kg bw/day; mortality at 700 mg/kg bw/day **Foetal:** Developmental delay (increased incidence of poor or non-ossified bones) at ≥ 350 mg/kg bw/day	**NOAEL:** Maternal: 50 mg/kg/day Foetal: 50 mg/kg/day	**LOAEL**: Maternal: 350 mg/kg/day Foetal: 350 mg/kg/day	[redacted] (1994)
Rabbit, NZW strain	Developmental toxicity (gavage)	Dimethachlor (CGA17020) technical Batch: OP. 110001 Purity: 96.8% w/w 0, 10, 100, 350, 600 mg/kg bw/day by oral gavage on gestation days 6-18 Vehicle 1.5% MC	**Maternal** Reduced body weight and food consumption **Foetal** No effects	**NOAEL**: Maternal: 100 mg/kg/day Foetal: 350 mg/kg/day	**LOAEL**: Maternal: 350 mg/kg/day Foetal: not determined	[redacted] (1993)

2.6.10.1 Toxicological end point for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake)

The acceptable daily intake (ADI) is derived from the NOAEL in the most susceptible species, usually from repeated dose toxicity studies with the application of an appropriate safety factor. A summary of all studies relevant for setting the ADI is given in table 60.
In the long-term studies body weight effects were noted in rat and mouse and kidney and liver were the target organs. In the 90 day dog studies increased liver weights, clinical pathology changes and histopathological changes in the liver identified the liver as the target organ. A NOAEL of 11.1 mg/kg bw/day, from the 2-year chronic toxicity/carcinogenicity study in rats is considered the most appropriate study for the estimation of the ADI of dimethachlor in humans, supported by the 90 day dog study. An uncertainty factor of 100 (for interspecies variations and an intraspecies variations) is applied to the NOAEL of 11.1 mg/kg bw/day, resulting in an ADI of 0.1 mg/kg bw/day.

$$ADI_{systemic} = \frac{NOAEL\ (2\ year,rat)}{SF} = \frac{11.1\ mg/kg\ bw/day}{100} = 0.1\ mg/kg\ bw/day$$

Endpoint	EU agreed endpoint (EFSA Scientific Report (2008) 169, 1-111, Conclusion on the peer review of dimethachlor)
ADI (mg/kg bw/day)	0.1 mg/kg bw/day (2 year rat, supported by 90 day dog)

2.6.10.2 Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

The Acute Reference Dose is an estimate of the amount of a substance in food or drinking water that can be ingested in a period of 24 hours or less, without appreciable health risk to consumers. A summary of all studies relevant for setting the ARfD is given in table 60.
The developmental toxicity study in the rat was considered for the derivation of the ARfD based on mortality observed in dams in the rat developmental toxicity study at 700 mg/kg/day, and decreased body weight gain and food consumption at ≥ 350 mg/kg/day, a NOAEL of 50 mg/kg bw/day was set in this study. An uncertainty factor of 100 (for interspecies variations and an intraspecies variations) is applied to the NOAEL of 50 mg/kg bw/day, resulting in an ARfD of 0.5 mg/kg bw.

$$ARfD_{systemic} = \frac{NOAEL\ developmental,rat)}{SF} = \frac{50\ mg/kg}{100} = 0.5\ mg/kg\ bw/day$$

Endpoint	EU agreed endpoint (EFSA Scientific Report (2008) 169, 1-111, Conclusion on the peer review of dimethachlor)
ARfD (mg/kg bw/day)	0.5 mg/kg bw/day (developmental toxicity study in rats)

2.6.10.3 Toxicological end point for assessment of occupational, bystander and residents risks – AOEL (acceptable operator exposure level)

Short-term studies, especially subchronic toxicity studies, are considered the most appropriate for the derivation of the AOEL. A summary of all studies relevant for setting the AOEL is given in table 6.5-1.
The liver was the main target organ in 90-day toxicity studies in rats, mice and dogs. The NOAELs from the two 90-day dog studies are considered the most appropriate for the derivation of the AOEL. Therefore, the AOEL is calculated based on the NOAEL of the 90-day dog studies of 10 mg/kg bw/day. An uncertainty factor of 100 (for interspecies variations and intraspecies variations) is applied to the NOAEL of 10 mg/kg bw/day. As the systemic absorption of dimethachlor after oral administration was determined to be ≥ 94 %, there is no requirement to adjust for absorption, resulting in an AOEL of 0.1 mg/kg bw/day.

$$AOEL_{systemic} = \frac{NOAEL\ (90\ day\ dog)}{SF} = \frac{10.1\ mg/kg}{100} = 0.1\ mg/kg\ bw/day$$

Endpoint	EU agreed endpoint EFSA Scientific Report (2008) 169, 1-111, Conclusion on the peer review of dimethachlor)
AOEL (mg/kg bw/day)	0.1 mg/kg bw/day (90 day dog)

2.6.10.4 Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL (acute acceptable operator exposure level)

An ARfD using the rat development toxicity study in rats was set at the last EFSA conclusion of dimethachlor and is still considered to be appropriate. This has been used to propose an acute AOEL (AAOEL) suitable for the assessment of operators exposed to the active substance under acute scenarios. As the systemic absorption of dimethachlor after oral administration was determined to be ≥ 94 %, there is no requirement to adjust for absorption.

$$AAOEL = \frac{NOAEL\ (developmental,rat)}{} =$$

$$\frac{50\ \mu g/\mu g\ \text{ai}/\text{day}}{100} = 0.5\ \text{mg/kg bw/day}$$

2.6.11 Summary of product exposure and risk assessment

Operators

Operator exposure for the representative formulation (A5089H) was assessed against the AOEL agreed in the EU review of dimethachlor and a proposed AAOEL, according to the Agricultural Operators Exposure Model (AOEM), as provided in the EFSA Guidance on non-dietary exposure assessment[12]. The results for the representative uses are summarised in the following table.

Table 61: Summary of estimated operator exposure to dimethachlor for A5089H

Model data	Level of PPE	Total systemic exposure			
		Longer term		Acute	
		mg/kg bw/d	% AOEL	mg/kg bw/d	% AAOEL
Vehicle-mounted sprayer application (downwards): oilseed rape *Application rate: 1 kg a.s./ha at 200L/ha (using 24% for dermal absorption for in-use dilution)*					
EFSA model • Crop type: oilseeds • 50 ha/day • 60 kg operator	No PPE; workwear (long sleeved shirt and trousers)	0.1129	113	0.4821	96.4
	Gloves during mixing and loading; workwear	0.0343	34.3	0.1905	38.1
Vehicle-mounted sprayer application (downwards): oilseed rape *Application rate: 1 kg a.s./ha at 300L/ha (using extrapolated 27% for dermal absorption for in-use dilution)*					
EFSA model • Crop type: oilseeds • 50 ha/day • 60 kg operator	No PPE; workwear (long sleeved shirt and trousers)	0.1167	117	0.5026	101
	Gloves during mixing and loading; workwear	0.0381	38.1	0.2111	42.2
Vehicle-mounted sprayer application (downwards): oilseed rape *Application rate: 0.75 kg a.s./ha at 200L/ha (using 24% for dermal absorption for in-use dilution)*					
EFSA model • Crop type: oilseeds • 50 ha/day • 60 kg operator	No PPE; workwear (long sleeved shirt and trousers)	0.0888	88.8	0.3861	77.2
	Gloves during mixing and loading; workwear	0.0258	25.8	0.1527	30.5
Vehicle-mounted sprayer application (downwards): oilseed rape *Application rate: 0.75 kg a.s./ha at 300L/ha (using extrapolated 36% for dermal absorption for in-use dilution)*					
EFSA model • Crop type: oilseeds • 50 ha/day • 60 kg operator	No PPE; workwear (long sleeved shirt and trousers)	0.1004	100	0.4526	90.5
	Gloves during mixing and loading; workwear	0.0374	37.4	0.2192	43.8

[12] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

According to the EFSA calculations, it can be concluded that the risk for the operator using A5089H for the proposed uses is acceptable with the use of standard workwear and additionally gloves worn during mixing and loading activities.

Bystander and resident exposure

Bystander and resident exposure for the representative formulation (A5089H) were assessed against the AOEL agreed in the EU review of dimethachlor and a proposed AAOEL, according to the Agricultural Operators Exposure Model (AOEM), as provided in the EFSA Guidance on non-dietary exposure assessment[13]. The results for the representative uses are summarised in the following table. A summary of the estimated bystander/resident exposures to dimethachlor is presented in tables below.

Table 62: Estimated bystander exposure to dimethachlor according to the EFSA guidance for A5089H

	Exposure Pathway (mg/kg bw/d)	Systemic exposure (mg/kg bw/d)	Exposure (% AAOEL)
Oilseed Rape – 1kgai/ha at 200L/ha			
Bystander – child	Spray drift (95th percentile)	0.0734	14.68
	Vapour (95th percentile)	0.0011	0.21
	Surface deposits (95th percentile)	0.0127	2.55
	Entry into treated crops (95th percentile)	0.0405	8.10
Bystander – adult	Spray drift (95th percentile)	0.0199	3.98
	Vapour (95th percentile)	0.0002	0.05
	Surface deposits (95th percentile)	0.0049	0.99
	Entry into treated crops (95th percentile)	0.0225	4.50
Oilseed Rape – 1kgai/ha at 300L/ha			
Bystander – child	Spray drift (95th percentile)	0.0550	11.00
	Vapour (95th percentile)	0.0011	0.21
	Surface deposits (95th percentile)	0.0141	2.81
	Entry into treated crops (95th percentile)	0.0456	9.11
Bystander – adult	Spray drift (95th percentile)	0.0149	2.98
	Vapour (95th percentile)	0.0002	0.05
	Surface deposits (95th percentile)	0.0055	1.11
	Entry into treated crops (95th percentile)	0.0253	5.06
Oilseed Rape – 0.75kgai/ha at 200L/ha			
Bystander – child	Spray drift (95th percentile)	0.0550	11.01
	Vapour (95th percentile)	0.0011	0.21
	Surface deposits (95th percentile)	0.0095	1.91
	Entry into treated crops (95th percentile)	0.0304	6.08
	Spray drift (95th percentile)	0.0149	2.98

[13] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

Bystander – adult	Vapour (95th percentile)	0.0002	0.05
	Surface deposits (95th percentile)	0.0037	0.74
	Entry into treated crops (95th percentile)	0.0169	3.38
Oilseed Rape – 0.75kgai/ha at 300L/ha			
Bystander – child	Spray drift (95th percentile)	0.0549	10.98
	Vapour (95th percentile)	0.0011	0.21
	Surface deposits (95th percentile)	0.0135	2.71
	Entry into treated crops (95th percentile)	0.0456	9.11
Bystander – adult	Spray drift (95th percentile)	0.0149	2.98
	Vapour (95th percentile)	0.0002	0.05
	Surface deposits (95th percentile)	0.0055	1.11
	Entry into treated crops (95th percentile)	0.0253	5.06

Table 63: Estimated residential exposure to dimethachlor according to the EFSA guidance for A5089H

	Exposure Pathway (mg/kg bw/d)	**Systemic exposure (mg/kg bw/d)**	**Exposure (% AOEL)**
Oilseed Rape – 1kgai/ha at 200L/ha			
Resident – child	Spray drift (75th percentile)	0.0323	32.29
	Vapour (75th percentile)	0.0011	1.07
	Surface deposits (75th percentile)	0.0043	4.31
	Entry into treated crops (75th percentile)	0.0405	40.50
	All pathways (mean)	0.0543	54.31
Resident – adult	Spray drift (75th percentile)	0.0077	7.72
	Vapour (75th percentile)	0.0002	0.23
	Surface deposits (75th percentile)	0.0016	1.64
	Entry into treated crops (75th percentile)	0.0225	22.50
	All pathways (mean)	0.0230	23.03
Oilseed Rape – 1kgai/ha at 300L/ha			
Resident – child	Spray drift (75th percentile)	0.0242	24.21
	Vapour (75th percentile)	0.0011	1.07
	Surface deposits (75th percentile)	0.0047	4.74
	Entry into treated crops (75th percentile)	0.0456	45.56
	All pathways (mean)	0.0542	54.21
Resident – adult	Spray drift (75th percentile)	0.0058	5.79
	Vapour (75th percentile)	0.0002	0.23
	Surface deposits (75th percentile)	0.0018	1.84
	Entry into treated crops (75th percentile)	0.0253	25.31
	All pathways (mean)	0.0245	24.51

Oilseed Rape – 0.75kgai/ha at 200L/ha			
Resident – child	Spray drift (75th percentile)	0.0242	24.22
	Vapour (75th percentile)	0.0011	1.07
	Surface deposits (75th percentile)	0.0032	3.23
	Entry into treated crops (75th percentile)	0.0304	30.38
	All pathways (mean)	0.0410	41.00
Resident – adult	Spray drift (75th percentile)	0.0058	5.79
	Vapour (75th percentile)	0.0002	0.23
	Surface deposits (75th percentile)	0.0012	1.23
	Entry into treated crops (75th percentile)	0.0169	16.88
	All pathways (mean)	0.0173	17.33
Oilseed Rape – 0.75kgai/ha at 300L/ha			
Resident – child	Spray drift (75th percentile)	0.0242	24.19
	Vapour (75th percentile)	0.0011	1.07
	Surface deposits (75th percentile)	0.0045	4.54
	Entry into treated crops (75th percentile)	0.0456	45.56
	All pathways (mean)	0.0540	54.05
Resident – adult	Spray drift (75th percentile)	0.0058	5.79
	Vapour (75th percentile)	0.0002	0.23
	Surface deposits (75th percentile)	0.0018	1.84
	Entry into treated crops (75th percentile)	0.0253	25.31
	All pathways (mean)	0.0245	24.51

According to the model calculations, it can be concluded that there is no undue risk to the bystander or resident after incidental exposure to A5089H.

Workers

Worker exposure assessment was carried out according to the EFSA guidance[14] on non-dietary exposure assessment for crop inspection, which is considered to be the relevant scenario for the proposed uses on oilseed rape. A summary of the estimated worker exposure to dimethachlor is presented below.

Table 64: Estimated worker exposure to dimethachlor

[14] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

Crop	Potential exposure level	Estimated exposure	
		mg/kg bw/d	% AOEL
Application rate: 1 kg a.s./ha at 200L/ha			
Oilseed rape (crop inspection)	Total exposure (adequate work clothing)	0.0336	33.6
Application rate: 1 kg a.s./ha at 300L/ha			
Oilseed rape (crop inspection)	Total exposure (adequate work clothing)	0.0378	37.8
Application rate: 0.75 kg a.s./ha at 200L/ha			
Oilseed rape (crop inspection)	Total exposure (adequate work clothing)	0.0252	25.2
Application rate: 0.75 kg a.s./ha at 300L/ha			
Oilseed rape (crop inspection)	Total exposure (adequate work clothing)	0.0378	37.8

According to the model calculations, it can be concluded that no unacceptable risk is anticipated for the worker wearing adequate clothing (but no PPE), when re-entering crops treated with A5089H for crop inspection activities. As a standard rule, it should be specified on the label that treated crops should not be re-entered before spray deposits on leaf surfaces have completely dried.

2.7 RESIDUE

2.7.1 Summary of storage stability of residues

Two studies assessing the stability of dimethachlor under freezer storage conditions have been previously evaluated at EU level (see DAR, 2007 and EFSA, 2008). Only one of them was performed under GLP. Control samples of oilseed rape were spiked with 0.5 mg/kg dimethachlor. Residues of dimethachlor in rape seeds stored at or below -18 ºC proved to be stable over the tested period of 24 months. The non-GLP study confirmed this result.

New storage stability data have been generated for renewal of approval to support storage of samples of dimethachlor and four metabolites (CGA50266, CGA354742, SYN551032 and CGA048090) analysed in new field crop rotation trials.

Residues of dimethachlor and its metabolites CGA50266 and CGA354742 can be assumed to be stable in lettuce head (high water), wheat grain (high starch), oilseed rape seeds (high oil), dried broad beans (high protein) and orange whole fruit (high acid) matrices when stored at ≤ -18°C for a minimum of 24 months.

Residues of SYN551032 and CGA048090 can be assumed to be stable in lettuce head (high water), wheat grain (high starch), oilseed rape seeds (high oil), dried broad beans (high protein) and orange whole fruit (high acid) matrices when stored at ≤ -18°C for a minimum of 1 month. Study is ongoing with the final report expected October 2021.

Table 65: Overview of residue storage stability data

Plant products (available studies)	**Category**	**Commodity**	**T** (°C)	**Stability period**		**Compounds covered**	**Comment/Source**
				Value	**Unit**		
	High water content	Lettuce	-18ºC	24 (732) 1 (30) 1 (34)	months (days)	Dimethachlor, CGA50266, CGA354742 SYN551032 CGA048090	

	High oil content	Oilseed rape	-18ºC	24 (735) 1 (34) 1 (33)	months (days)	Dimethachlor, CGA50266, CGA354742 SYN551032 CGA048090	Interim report is available providing information on storage stability of 1 month for SYN551032 and CGA048090 at -18ºC.
	High protein content	Dried broad beans	-18ºC	24 (740) 1 (28) 1 (33)	months (days)	Dimethachlor, CGA50266, CGA354742 SYN551032 CGA048090	
	High starch content	Wheat grain	-18ºC	24 (728) 1 (28) 1 (29)	months (days)	Dimethachlor, CGA50266, CGA354742 SYN551032 CGA048090	
	High acid content	Orange whole fruit	-18ºC	24 (726) 1 (28) 1 (34)	months (days)	Dimethachlor, CGA50266, CGA354742 SYN551032 CGA048090	
	Processed products						
	Others						

Table 66: Overview of storage of samples pior to analysis

Test item	**Samples**	**Max. storage period**
Dimethachlor (CGA17020)	Seed	632 d
	Whole plant	433 d

As residues are shown to be stable in all commodities studied, a study on one commodity from each of the five commodity categories is acceptable. Therefore, residues in all other commodities (see Annex 1 of OECD 506) would be assumed to be stable for the same duration of time under the same storage conditions.

2.7.2 Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

Metabolism in Plants

Two studies assessing the metabolic behaviour of dimethachlor in plants have been previously evaluated at EU level, one in oilseed rape (pre-emergence) and one in soybean (see DAR, 2007 and EFSA, 2008). Only the study on oilseed rape was performed under GLP; it is still considered to be scientifically valid.
At maturity (294 days after application), the total residues in seeds amounted to 0.051 mg/kg. The total radioactive residue (TRR) was characterised as a multitude of minor degradation products in the range of 0.001-0.006 mg/kg. In seeds at plant maturity, parent dimethachlor was not detectable while the two minor metabolites CGA 50266 (0.004 mg/kg) and CGA 39981 (0.001 mg/kg) were identified. These two metabolites are major soil metabolites in the upper soil layers and may have a direct soil origin. According to the results of the metabolism study, after soil

application on rapeseed, dimethachlor is converted directly or through the glutathione conjugate pathway to CGA 39981, and then to CGA 50266.
The study on soybean is not further relied upon as no metabolite identification was conducted.
A new metabolism study on oilseed rape has been performed with post-emergence application to cover also the post-emergence use on oilseed rape. After post-emergence soil application, total radioactive residues were determined in all commodities harvested and ranged from 0.051 mg/kg in the seed commodity up to 2.768 mg/kg in the foliage sample at day 18.
Metabolism of parent dimethachlor was extensive and complete (parent was not detected). The 3-thiolactic acid sulfoxide metabolite (SYN550004) was the principal metabolite identified in foliage (46.8% TRR; 3.261 mg/kg; co-eluting with lower levels of SYN547047).
Other identified metabolites were found at much lower levels (a maximum of 8.1% TRR; 0.564 mg/kg for the malonyl cysteine conjugate U4 in foliage). Residue levels were much lower in the seed compared to the foliage, with only one metabolite present at ≥ 0.01 mg/kg in the seed (SYN547047; 5.3% TRR, 0.010 mg/kg).
Natural incorporation of 14C into crop endogenous constituents was observed and confirmed by the detection of 14C-oleic acid.

Metabolism in Animals

Dimethachlor is intended for use on oilseed rape, commodities which might be fed to livestock. Since all residues in feed commodities were low (<LOQ), the calculated dietary burdens for ruminants were found to be below the trigger value of 0.004 mg/kg bw/day, further investigation on metabolism of residues in animals in not necessary.

2.7.3 Definition of the residue

The current definitions of residue in crops for dimethachlor for monitoring and risk assessment is dimethachlor; pending further investigation on the metabolism in rotational crops highlighted during the original peer review, the same residue definition as for primary crops was tentatively proposed for crops grown in rotation (EFSA 2008. and 2016.).
As significant exposures to dimethachlor are not expected for any group of livestock, the further investigation of residues, as well as the setting of MRLs in commodities of animal origin, has previously been concluded as not being necessary (EFSA 2008. and 2016.).

Use pattern
Dimethachlor, i.e. 2-chloro-N-(2,6-dimethyl-phenyl)-N-(2-methoxy-ethyl)-acetamide (IUPAC), CAS-No.50563-36-5, is an herbicide active against annual grasses and annual broad-leaved weeds. It is mainly used in winter/spring oilseed rape cultures at an application rate of max. 1 kg as/ha. Spraying is recommended at pre-emergence stage and early post-emergence of the crop (BBCH 00-20).
Dimethachlor, like other chloracetanilides, can penetrate easily into weed shoot to react with nucleophilic sites of essential plant components. Resulting inhibition of VLCFA (very long chain fatty acid) synthesis, for example, is considered as a major cause of phytotoxicity. As a consequence dimethachlor inhibits cell division, and further seed germination and weed growth.

Identification of critical GAPs
For dimethachlor only one GAP in oil seed rape for Europe is proposed. This GAP is considered as critical case and is presented in chapter B.3.2 (1 application at BBCH 00-20, 1 kg as/ha, 80-400 L water/ha, PHI: F).

Plant Commodities – Primary Crops
The metabolism in plant has been investigated in winter rape. An additional study with soybeans was submitted, in which the uptake, translocation and degradation in young plants were analysed. The main uptake of dimethachlor occurs via the roots of the plants. The soil metabolites CGA 50266 and CGA 39981 could also be identified in mature plant material. As a main degradation pathway the parent substance in conjugated with gluthathion. In the following the gluthathion pathway leads to further breakdown products in minor quantities (< 10 % of TRR and < 1.1 mg/kg each).
A new metabolism study on oilseed rape has been performed with post-emergence application to cover also the post-emergence use on oilseed rape. Residues of parent dimethachlor in oilseed rape are expected to be low as the metabolism of parent dimethachlor was extensive and complete (parent was not detected). The high residues of SYN550004 in oilseed rape foliage are not relevant for human consumption and no use of oilseed forage as an animal feed is requested. The study supports the representative post-emergence use on oilseed rape.
Based on new primary crop metabolism studies on oilseed rape and field crop residue trials conducted on oilseed rape generated since the original peer review, the current definitions of residue in crops for monitoring and risk assessment of dimethachlor is still appropriate to primary crops (limited to pulses and oilseeds).

In the primary crop metabolism study [Phenyl-U-^{14}C]-Dimethachlor was applied post-emergence by foliar spray application to oilseed rape plants at a rate of 1000 g a.s./ha at growth stage BBCH 16 (leaf development, 6 leaves unfolded). Oilseed rape commodities were harvested at two growth stages: foliage at BBCH 35-39 and the mature crop separated into seeds and trash at crop maturity (BBCH 89), 84-105 days after application.
The key observations from identification work were as follows:

- Metabolism of parent dimethachlor was extensive and complete (parent was not detected);
- The 3-thiolactic acid sulfoxide metabolite (SYN550004) was the principal metabolite identified in foliage (46.8% TRR; 3.261 mg/kg; co-eluting with lower levels of SYN547047);
- Other identified metabolites were found at much lower levels (a maximum of 8.1% TRR; 0.564 mg/kg for the malonyl cysteine conjugate U4 in foliage);
- Residue levels were much lower in the seed compared to the foliage, with only one metabolite present at ≥ 0.01 mg/kg in the seed (SYN547047; 5.3% TRR, 0.010 mg/kg);
- Natural incorporation of ^{14}C into crop endogenous constituents was observed and confirmed by the detection of ^{14}C-oleic acid.

In a pre-emergence primary crop metabolism study, [Phenyl-U-^{14}C]-Dimethachlor (CGA17020) was applied to the soil three days after sowing of the oilseed rape seeds. Oilseed rape plant samples were harvested 18 days after application (dicotyledons + 2 leaves stage, BBCH 12) and 32 days after application (dicotyledons + 4 leaves stage, BBCH 14). Plant samples were also harvested at 222 days after application (blooming stage, ~BBCH 65) and 294 days after application (maturity, BBCH 89). At maturity, all plant samples were separated into stalks, pods and seeds.

- In all plant parts and across all sampling intervals, parent dimethachlor was below the limit of detection (<0.001 mg/kg), i.e. not detectable.

The metabolic pathways are consistent between the two primary metabolism studies conducted on oilseed rape. The only commodity for human consumption is oilseed rape seed, and all metabolites observed, were below the trigger level of 10% of the TRR (OECD, 2009)*15*.
A total of 51 field crop residue trials conducted on oilseed rape at an application rate of 750-1500 g a.s./ha with pre- and post-emergent applications demonstrate that all residues of dimethachlor in the oilseed rape seed samples are below the limit of quantification (<0.01 or <0.02 mg/kg), consistent with the metabolism studies.
Taking account of all the data presented it is proposed to maintain the current EU residue definitions in primary crop commodities for risk assessment and monitoring purposes as parent dimethachlor only. The residues of parent dimethachlor can be determined using standard methodologies e.g. QUECHERS multi-residue method (LC-MS/MS).

Plant Commodities – Rotated Crops
Based on a new confined rotational crop study and field rotational crop studies generated since the original peer review and taking into account data from the rat metabolism study, as well as from toxicology studies on metabolites, the current definitions of residue in crops for monitoring and risk assessment of dimethachlor is still appropriate to rotated crops.
In the confined rotational crop study, following a single application of [phenyl-U-^{14}C]-dimethachlor to bare soil at a nominal rate of 1000 g a.s./ha, uptake, distribution and metabolism of residues of dimethachlor was investigated on three indicator crops, barley, turnip and pak choi that were sown in the treated soil after periods of 30, 119 and 273 days.
The results indicated that:

- Residues were generally the highest in commodities from the 30 DAA rotational interval and decreased at the following intervals (119 and 273 DAA);
- No parent (dimethachlor) was detected in any sample above the limit of quantification;
- Biotransformation products were consistent across the commodities analysed.

Overall, three major biotransformation products of dimethachlor were detected:

- CGA50266 was found in all samples from all intervals with the exception of the barley grain samples from the 119 and 273 DAA rotational intervals. CGA50266 was the most abundant metabolite in most of the samples with the highest absolute levels found in barley hay from the 30 DAA rotational interval (16.6% TRR, 0.741 mg/kg) and the highest relative levels found in pak choi mature leaves from the 273 DAA rotational interval (64.7% TRR, 0.029 mg/kg).
- SYN551032 was found in the majority of the commodities with the exception of barley grain samples at 119 and 273 DAA and turnip roots at 30 DAA. Highest absolute levels were found in barley hay from the 30 DAA rotational interval (10.7% TRR, 0.475 mg/kg) and the highest relative levels in barley hay from

15 **OECD Guidance Document on the Definition of Residue ENV/JM/MONO(2009)30** *(…..Minor Metabolites. Metabolites or degradates that comprise less than 10% of the TRR are classified as minor metabolites or degradates. Minor metabolites are typically not included in the dietary risk assessment, as they generally do not contribute significantly to the exposure.)*

the 30 DAA rotational interval (18.4% TRR, 0.146 mg/kg).

- A glucose conjugate of CGA048090 was found in barley forage and hay, turnip leaves and pak choi commodities with the highest absolute levels found in barley hay at the 119 DAA rotational interval (2.8% TRR, 0.047 mg/kg) and the highest relative levels found in turnip leaves from the 119 DAA rotational interval (12.4% TRR, 0.042 mg/kg).

Other (minor) metabolites detected included CGA354742, SYN547047, CGA42443, CGA48086 and CGA102935.
Four rotational crop residue field trials on rotated crops were conducted in the UK, Germany, Southern France and Spain. Dimethachlor was applied as a single application to bare soil at a rate of 1500 g a.s./ha in all treated sub-plots.
Three representative rotated crops were chosen (spinach, carrot and spring barley) which were planted to subplots at designated timings. The nominal plantback timings for each crop were 30, 60, 270 and 365 days after the last application.
Samples of spinach (leaves), carrot (roots, tops) and spring barley (whole plant, grain and straw) were analysed for dimethachlor, CGA50266, CGA354742, SYN551032 and CGA048090. The residues observed are summarized in the table below scaled from 1500 g a.s./ha to the proposed application rate of 1000 g a.s./ha.

Table 67: Residues in rotational crops at application rate of 1000 g a.s./ha

	Spinach (mg/kg)	**Carrot Roots (mg/kg)**	**Carrot Tops (mg/kg)**	**Barley Grain (mg/kg)**	**Barley Whole Plant (mg/kg)**	**Barley Straw (mg/kg)**
Dimethachlor (CGA17020)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
CGA50266	<0.01-0.06	<0.01	<0.01	<0.01	<0.01-0.03	<0.01
CGA354742	<0.01-0.05	<0.01	<0.01-0.01	<0.01	<0.01-0.02	<0.01-0.02
SYN551032	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
CGA048090	<0.01-0.02	<0.01	<0.01-0.01	<0.01	<0.01	<0.01

CGA50266
Residues of CGA50266 were below the limit of quantification (i.e. <0.01 mg/kg) in carrot root, and barley grain and were generally low in spinach (<0.01-0.06). Residues in animal feed commodities were also generally low (<0.01-0.03 mg/kg in barley whole plant; <0.01 mg//kg in barley straw and carrot tops). Toxicological data on metabolite CGA50266 are available and the results are described in detail in the Volume 3 – B.6 (AS) Toxicology and metabolism data. CGA50266 is not acutely toxic following oral administration (LD_{50} > 2000 mg/kg bw). *In vitro* genotoxicity studies show there was no evidence of mutagenicity or clastogenicity. In the 3-month subchronic studies for CGA50266 and dimethachlor, the NOAEL was 400 mg/kg bw/day for CGA50266 compared with a NOEL of 2.21 mg/kg bw/day for dimethachlor. It is therefore concluded that CGA50266 is less toxic than parent dimethachlor. Therefore, it is proposed to not include metabolite CGA50266 in the consumer risk assessment owing to low exposure in rotated crops and low relative toxicity compared to parent dimethachlor.

SYN551032
Residues of SYN551032 were below the limit of quantification (i.e. <0.01 mg/kg) in all food and feed commodities, hence indicating no unacceptable concern for consumer exposure. For SYN551032, no genotoxicity data is available and the metabolite is considered structurally different to all other metabolites of dimethachlor. SYN551032 is chemically and structurally similar to CGA50720, a groundwater metabolite of S-metolachlor. CGA50720 is not considered to be of genotoxic concern and has a full negative genotoxicity package available. Details of the read-across argument can be found in the Volume 3 – B.6 (AS) Toxicology and metabolism data. Therefore read-across for genotoxicity data from CGA50720 to SYN551032 is supported. SYN551032 is not considered to be of genotoxic concern. Therefore, it is considered unnecessary to include metabolite SYN551032 in the definition of residue for consumer risk assessment or monitoring.

CGA354742
In the field crop rotation studies, residues of CGA354742 were below the limit of quantification (i.e. <0.01 mg/kg) in carrot root and barley grain. Residues of CGA354742 in spinach were also generally low (<0.01-0.05 mg/kg). Residues in animal feed commodities were generally low (<0.01-0.02 mg/kg in barley whole plant and straw and

<0.01-0.01 mg/kg in carrot tops). Toxicological data on metabolite CGA354742 are available and the results are described in detail in the Volume 3 – B.6 (AS) Toxicology and metabolism data CGA354742 is not acutely toxic following oral administration (LD50 > 2000 mg/kg bw). *In vitro* genotoxicity studies show there was no evidence of mutagenicity or clastogenicity. In the 3-month subchronic studies for CGA354742 and dimethachlor, the NOAEL was 69.6 mg/kg bw/day for CGA354742 compared with a NOEL of 2.21 mg/kg bw/day for dimethachlor. It is therefore concluded that CGA354742 is considered less toxic than parent. Therefore, it is proposed to not include metabolite CGA354742 in the consumer risk assessment owing to low exposure in rotated crops and relative toxicity compared to parent dimethachlor.

CGA048090
Residues of CGA048090 were below the limit of quantification (i.e. <0.01 mg/kg) in carrot root and barley grain and were also generally low in spinach (<0.01-0.03). Residues in animal feed commodities were generally low in barley whole plant and straw (<0.01 mg//kg) and <0.01-0.01 mg.kg in carrot tops). CGA048090 has been identified in rat metabolism study at <5.4%. No toxicological data has been generated for CGA048090; however, the concern for genotoxicity and general toxicity can be addressed through QSAR and read-across to CGA354742. Details of the QSAR and read-across argument can be found in the Volume 3 – B.6 (AS) Toxicology and metabolism data It is therefore concluded that CGA048090 is considered less toxic than parent. Therefore, it is proposed to not include metabolite CGA048090 in the consumer risk assessment owing to low exposure in rotated crops and relative toxicity compared to parent dimethachlor.
Taking account of all the data presented it is proposed to maintain the current EU residue definitions in rotated crop commodities for risk assessment and monitoring as parent dimethachlor only. Residues of parent dimethachlor can be determined using standard methodologies e.g. QUECHERS multi-residue method (LC-MS/MS).

Plant Commodities – Processed Commodities
Since residues of dimethachlor were shown to be below the limit of quantification in the representative use on oilseed rape, further investigation of the effect of processing on the magnitude of residues is therefore not required. The proposed definition of residue for crops (parent dimethachlor) is sufficient.
Animal Commodities
In potential feeding stuffs only minor amounts of residues from the application of dimethachlor are detectable.
Since the calculated dietary burdens were all found to be below the trigger value of 0.004 mg/kg bw/day, further investigation of residues, metabolism studies on livestock animals, as well as the setting of MRLs in commodities of animal origin, is unnecessary. A residue definition for animal products is not proposed.

Table 68: EU Conclusion - Definition of Residue for Dimethachlor

Endpoint	EU agreed endpoint (EFSA 2008)	Proposed endpoint
Definition of the residue in crops (for MRL-setting purposes)	Dimethachlor provisional	Dimethachlor (pulses and oilseeds only)
Definition of the residue in crops (for risk assessment purposes)	Dimethachlor	Dimethachlor (pulses and oilseeds only)
Definition of the residue in animal products (for MRL-setting purposes)	No residue definition required	No change
Definition of the residue in animal products (for risk assessment purposes)	No residue definition required	No change

2.7.4 Summary of residue trials in plants and identification of critical GAP

The representative use in the first EU evaluation of dimethachlor was pre-emergent use in winter oilseed rape in Northern Europe with a single application of 1500 g/ha. Of the 51 residue trials included in this submission, 18 were conducted on oilseed rape after pre- or early post-emergence application of dimethachlor in Northern Europe and have been previously evaluated at the EU level (see DAR, 2007 and EFSA, 2008). In these 18 residue trials, only one positive residue of dimethachlor was detected at 0.05 mg/kg. It was concluded that the residue at 0.05 mg/kg is not a correct result and perhaps was due to a matrix component or sample contamination (EFSA, 2008).

18 new residue trials have been conducted to support the pre- or post-emergence application of dimethachlor on oilseed rape in Northern Europe.

16 new residue trials have been conducted to support the pre- or post-emergence application of dimethachlor on oilseed rape in Southern Europe.

Table 69: Overview of the available dimethachlor on spring oilseed rape residues trials data

Commodity	Residue region, Outdoor /Indoor	Reviewed/ new	Individual trial results (mg/kg)		STMR (mg/kg)	HR (mg/kg)	MRL[b] (mg/kg)	Median CF
			Enforcement[a]	Risk assessment[a]				
Oilseed rape seed	NEU, outdoor	New	**GAP: 1x 1000 g a.s./ha, BBCH 00-01 (pre-emergent)**		0.01	0.01	0.01*[c]	-
			5× <0.01	5× <0.01				
		Reviewed	**GAP: 1x 1500 g a.s./ha, BBCH 07 (pre-emergent)**		0.02	0.02	0.02*[c]	-
			2× <0.02	2× <0.02				
		New and reviewed	**GAP: 1x 1000-1500 g a.s./ha, BBCH 00-07 (pre-emergent)**		**0.01**	**0.02**	**0.02*[c]**	**-**
			5x <0.01, 2 x <0.02	5x <0.01, 2 x <0.02				

Table 70: Overview of the available dimethachlor residues trials data to support winter oilseed rape

Commodity	Residue region, Outdoor /Indoor	Reviewed/ new	Individual trial results (mg/kg)		STMR (mg/kg)	HR (mg/kg)	MRL[(b)] (mg/kg)	Median CF
			Enforcement[(a)]	Risk assessment[(a)]				
Oilseed rape seed	NEU, outdoor	New	**GAP: 1x 750-1000 g a.s./ha, BBCH 00-05 (pre-emergent)**		0.01	0.02	0.02*[(d)]	-
			4× <0.02	4× <0.02				
			GAP: 1x 1000-1500 g a.s./ha, BBCH 12-39 (post-emergent)					
			9× <0.01	9× <0.01				
	SEU, outdoor		**GAP: 1x 750-1500 g a.s./ha, BBCH 00 (pre-emergent)**		0.02	0.02	0.02*[(d)]	-
			9× <0.02	9× <0.02				
			GAP: 1x 1000-1500 g a.s./ha, BBCH 13-30 (post-emergent)					
			7× <0.01	7× <0.01				
	NEU, outdoor	Reviewed[(c)]	**GAP: 1x 1500 g a.s./ha, BBCH 00-07 (pre-emergent)**		0.02	0.02	0.02*[(d)]	-
			4× <0.01 11× <0.02	4× <0.01 11× <0.02				
	NEU, SEU outdoor	New and reviewed	**GAP: 1x 750-1500 g a.s./ha, BBCH 00-07 (pre-emergent)**		0.02	0.02	0.02*[(d)]	-
			4x <0.01, 24× <0.02	4x <0.01, 24× <0.02				
			GAP: 1x 1000-1500 g a.s./ha, BBCH 12-39 (post-emergent)					
			16× <0.01	16× <0.01				

In none of the residue trials residues above the LOQ (<0.01 mg/kg and <0.02 mg/kg) could be determined in seeds. In whole plant part, residues in some residue trials were above LOQ, generally low with range of 0.01-0.018 mg/kg. The results of the additional/new residue trials are in good accordance to the residue trials evaluated during the Annex I inclusion process.

IDENTIFICATION OF CRITICAL GAPS

For dimethachlor only one GAP in oil seed rape for Europe is proposed. This GAP is considered as critical case and is presented in chapter B.3.2 (1 application at BBCH 00-20, 1 kg as/ha, 80-400 L water/ha, PHI: F).

Summary of representative uses evaluated (Dimethachlor, Annex I inclusion)

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Winter oil seed rape	EU	Teridox 500 EC A-5089 F/H	F	grasses and dicot weeds	EC	500 g/L	broad-cast spray applica-tion	pre- emer-gence BBCH 00-09	1	n.a.	-	100 - 400	1.5	n.a.	

Remarks:

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(i) g/kg or g/L
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

AIR Representative GAP

Crop and/or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Formulation**		**Application**				**Application rate per treatment**			**PHI** (days) (l)	**Remarks:** (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	g,kg as/ha min max		
Winter oil seed rape	EU	Teridox 500 EC A-5089 F/H	F	Grasses and dicot weeds	EC	Dimethachlor 500 g/L	broad-cast spray applica-tion	**pre- and early post emergence Crop-BBCH 00 – 20**	1	n.a.	-	**80 - 400**	**1000 g/ha**	n.a.	Total dose max. 1000 g dimethachlor/ha in a three-year period on the same field

Remarks:

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(i) g/kg or g/L
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

2.7.5 Summary of feeding studies in poultry, ruminants, pigs and fish

Dimethachlor is proposed for use on crops that might be fed to livestock. The median and maximum dietary burdens were therefore calculated for the different groups of livestock using the EFSA Animal Model 2017 tool (*pesticides_mrl_guidelines_animal_model_2017*). The input values for all relevant commodities have been selected according to the recommendations of the tool/ relevant guidance and are summarized in the following table and the dietary burden calculation is included below.

Table 71: Dimethachlor residues values used for calculation of livestock dietary burdens

Feed commodity	Median dietary Burden		Max dietary Burden	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Risk assessment residue definition: dimethachlor				
Rape, meal	0.02*	STMR[(a)]	0.02*	STMR[(a)]
Canola, meal	0.02*	STMR[(a)]	0.02*	STMR[(a)]

STMR: supervised trials median residue
*Indicates that the input value is proposed at the limit of quantification
(a) For oilseed meals, a default processing factor of 1 was applied because dimethachlor is applied early in the growing season and residues are expected to be below the LOQ. Concentration of residues in these commodities is therefore not expected.

The results of the dietary burden calculations are reported in the following table:

Table 72: Calculated maximum and median animal dietary burdens of Dimethachlor residues

Relevant groups	Dietary burden expressed in				Most critical diet[(a)]	Most critical commodity [(b)]		Trigger exceeded (Yes/No) 0.004 mg/kg bw
	mg/kg bw per day		mg/kg DM					
	Median	Maximum	Median	Maximum				
Cattle (all diets)	0.0001	0.0001	0.0045	0.0045	Beef cattle	Rape	meal	No
Cattle (dairy only)	0.0001	0.0001	0.0023	0.0023	Dairy cattle	Canola	meal	No
Sheep (all diets)	0.0001	0.0001	0.0034	0.0034	Lamb	Rape	meal	No
Sheep (ewe only)	0.0001	0.0001	0.0034	0.0034	Ram/Ewe	Rape	meal	No
Swine (all diets)	0.0001	0.0001	0.0045	0.0045	Swine (finishing)	Canola	meal	No
Poultry (all diets)	0.0003	0.0003	0.0045	0.0045	Turkey	Canola	meal	No
Poultry (layer only)	0.0002	0.0002	0.0023	0.0023	Poultry layer	Canola	meal	No

[(a)]When several diets are relevant (e.g. cattle, sheep and poultry "all diets"), the most critical diet is identified from the maximum dietary burdens expressed as "mg/kg bw per day"
[(b)]The most critical commodity is the major contributor identified from the maximum dietary burden expressed as "mg/kg bw per day".

Since dietary burdens are not >0.004 mg/kg bw/d for any of the animal in Table 72, animal metabolism and feeding studies are not required and thus default MRLs are applicable.

Fish

The use of dimethachlor results in residues <0.02 mg/kg for all feed commodities and the log Pow of dimethachlor is 2.17. Therefore, it is considered highly unlikely that significant residues will occur in fish following the use of dimethachlor in crops which may then be fed to fish.
Two literature papers related to dimethachlor residues in fish were identified during the AIR literature review (K-CA 6.4.4/01 and K-CA 6.4.4/02). Dimethachlor residues were below the limit of detection (LOD; value not reported) in

all fish muscle tissue samples and low accumulation through food exposure was observed and modeled. These literature papers support the postion above that it is highly unlikely that significant residues will occur in fish due to the use of dimethachlor on crops.

2.7.6 Summary of effects of processing

Studies investigating the effect of processing on the nature of the residue are not available and not required. Considering that quantifiable residues were not found in the commodities under assessment and that the chronic exposure does not exceed 10% of the acceptable daily intake (ADI), such studies are not necessary.

2.7.7 Summary of residues in rotational crops

Metabolism in rotational crops

A study assessing the metabolic behaviour of dimethachlor in rotational crops has been previously evaluated at EU level (see DAR, 2007 and EFSA, 2008).
EFSA concluded that dimethachlor is not persistent in the soil, *i.e.* that the DT_{90} is < 100 days, but that there are relevant metabolites present in soil with much longer DT_{90} values (*e.g.* CGA 50266 with up to 195.5 days), and because the DT_{90} for the total bio-available residue will be much greater than 100 days, the need for a rotational crop metabolism study is triggered. A data gap was identified due to the lack of the 30-day PBI in the rotational crop metabolism for lettuce and radish (EFSA, 2008). Moreover, the need to further investigate the rate of degradation of another soil metabolite (CGA 102935) was identified during the peer review.

A new metabolism study on rotational crops has been conducted for renewal of approval to address the the deficiencies noted above and the data gaps identified by EFSA. This study supercedes the EU reviewed study, which is therefore no longer relied upon.
Following a single application of [phenyl-U-^{14}C]-dimethachlor to bare soil at 1038.8 g a.s./ha (986.6 g a.s./ha for the pak choi from the 30 DAA rotational interval), barley, turnip and pak choi were sown in the treated soil after periods of 30, 119 and 273 days.

The total radioactive residues (TRR) in all commodities analysed were > 0.01 mg/kg, thus further analyses were undertaken to determine the nature of the constituent residues.

The highest TRR value was found in barley hay from the 30 DAA rotational interval (4.458 mg/kg) and the lowest TRR was found in turnip root from the 119 DAA rotational interval (0.024 mg/kg). TRR values declined progressively from rotational interval to rotational interval with the exception of barley grain, where slight increases were observed between 119 and 273 DAA.
No parent dimethachlor was detected in any sample and biotransformation products were consistent in the commodities analysed. CGA50266 was found in all samples from all intervals with the exception of the barley grain samples from the 119 and 273 DAA rotational intervals. SYN551032 was found in the majority of the commodities with the exception of barley grain samples at 119 and 273 DAA. A glucose conjugate of CGA048090 was found in barley forage and hay, turnip leaves and both pak choi commodities. Other minor metabolites detected included CGA354742, SYN547047, CGA42443, CGA48086 and CGA102935.

The results indicated that:

- Residues were generally the highest in commodities from the 30 DAA rotational interval and decreased at the following intervals;
- No parent (dimethachlor) was detected in any sample;
- Biotransformation products were consistent in the commodities analysed.

Residue metabolism in rotational crops is similar to the primary crop metabolism, therefore, the same residue definition applies to rotational crops.

Magnitude of residues in rotational crops

Field rotational crop studies were not available during the original EU review. Owing to residues >0.01 mg/kg in the confined crop rotation study, four rotational crop residue field trials on rotated crops have been conducted in the UK, Germany, Southern France and Spain. Dimethachlor was applied as a single application to bare soil at a rate of 1500 g a.s./ha in all treated sub-plots.

Three representative rotated crops were chosen (spinach, carrot and spring barley) which were planted to subplots at designated timings. The nominal plantback timings for each crop were 30, 60, 270 and 365 days after the last application. Samples of spinach, carrot and spring barley were collected from both trials.
In both trials dimethachlor and SYN551032 were not found in any succeeding crop at any of the plant back intervals and no residues of any metabolite were observed in carrot root or grain. Low levels of CGA50266, CGA354742 and CGA048090 were observed in some succeeding crops.

Residues storage stability studies for metabolites CGA50266, CGA354742, SYN551032 and CGA048090 are still ongoing. As storage stability for these metabolites has yet to be demonstrated, this rotational crop studies are informatory only until storage stability is confirmed by final reports.

2.7.8 Summary of other studies

2.7.8.1. Effect on the residue level in pollen and bee products

The data requirement objective of these studies is to determine the residue in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom.
Dimethachlor is used as an early application herbicide on oilseed rape only. Plant metabolism studies on oilseed rape demonstrate that in all plant parts and at all intervals, parent dimethachlor was always under the limit of quantification (<0.01 mg/kg).
In this study, dimethachlor was applied to oilseed rape at BBCH 16-19 at a nominal rate of 1000 g a.s./ha and residues analysed in pollen and nectar.
Pollen samples from oilseed rape flowers, retrieved by bees, were collected at the start (BBCH 61-64), middle (BBCH 64-65) and end (BBCH 65-69) of flowering.
Forager bees (nectar samples) were collected using modified hoovers at the start (BBCH 61-64), middle (BBCH 64-65) and end (BBCH 65-69) of flowering.
All residues of dimethachlor were below the limit of quantification (0.01 mg/kg) in both pollen and nectar. As the highest residue level measured in aerial parts of the crop at the time when the crop is foraged by bees is below 0.01 mg/kg, then the residue level expected in honey is assumed to be below the current EU MRL for dimethachlor on honey and other apiculture products (0.05* mg/kg).

2.7.9 Estimation of the potential and actual exposure through diet and other sources

The toxicological assessment of dimethachlor was peer reviewed under Directive 91/414/EEC and an ADI and ARfD were established by the European Commission (2009). A re-review of the toxicological data for dimethachlor has confirmed that the current ADI and ARfD are still appropriate (Volume 3 – B.6 (AS), Appendix I). The toxicological reference values used for dimethachlor are shown in following table:

Table 73: Toxicological reference values for Dimethachlor

Endpoint	EU agreed endpoint (EFSA 2008)
Acceptable Daily Intake (ADI)	0.1 mg/kg bw/d
Acute Reference Dose (ARfD)	0.5 mg/kg bw

Chronic exposure calculations for all crops proposed for dimethachlor were performed using revision 3.1 of the EFSA Pesticide Residues Intake Model (PRIMo). Detailed results of the calculations are presented in Annex 3.
The TMDI (Theoretical Maximum Daily Intake) calculation is derived based on existing EU MRLs.

Chronic risk assessment

Table 74: Chronic Risk Assessment Input Values

Code	Commodity	Chronic risk assessment	
		Input value (mg/kg)	Comment
0401060	Rapeseeds/canola seeds	0.02*	EU MRL (Reg. (EU) 2018/78)

MRL: Maximum Residue Level
*Indicates that the input value is proposed at the limit of quantification

Chronic exposure calculations for all crops proposed for dimethachlor were performed using revision 3.1 of the EFSA Pesticide Residues Intake Model (PRIMo). With the current EFSA model (PRIMo rev. 3.1) the maximum chronic risk assessment is 0.019% of the ADI of dimethachlor according to the proposed residue definition for risk assessment. The diet with the highest percent contribution to the ADI is NL toddler. For this diet, the highest contributor is rapeseeds/canola seeds.

Table 75: Chronic Risk Assessment Results

Risk Assessment	Dimethachlor
TMDI	0.019% of ADI (NL Toddler)

The above result indicates that there is no unacceptable chronic risk to human health from the consumption of commodities treated with dimethachlor according to the uses considered.

NEDI calculations

Considering the outcome of the chronic TMDI and associated contribution to the ADI, refinement of the risk assessment via consideration of STMR values is not deemed necessary.

Acute risk assessment

Table 76: Acute Risk Assessment Input Values

Code	Commodity	Acute risk assessment	
		Input value (mg/kg)	Comment
0401060	Rapeseeds/canola seeds	0.02*	HR (Article 12, 2016)[a]

*Indicates that the input value is proposed at the limit of quantification
[a]Oilseeds are a blended commodity, as such the STMR-RAC is appropriate for acute risk assessment.

With the current EFSA model (PRIMo rev. 3.1) the maximum acute risk assessment represents 0.006% of the ARfD of dimethachlor according to the proposed residue definition for risk assessment. The diet with the highest contribution to the ARfD is the DE child. For this diet, the highest contributor is rapeseeds/canola seeds. Results are presented in Table 77.

Table 77: Acute Risk Assessment Results

Risk Assessment	Dimethachlor
IESTI-RAC	0.006% of ARfD (DE Child)

Considering the outcome of the acute risk assessment and associated contribution to the ARfD, the results indicate that there is no unacceptable acute risk to human health from the consumption of commodities treated with dimethachlor according to the uses considered.

2.7.10 Proposed MRLs and compliance with existing MRLs

EU MRLs for dimethachlor are currently detailed in Annexes of Regulation (EC) No 396/2005.
The data presented in this document demonstrate that the proposed representative uses of dimethachlor do not lead to an exceedance of the recommended MRLs for oilseed rape.
EU MRLs for commodities relevant to the representative crop uses of dimethachlor are detailed in Table 78.

Table 78: Current and proposed EU MRLs for Dimethachlor for Representative Crops

Code	Commodity	Current EU MRL[a] (mg/kg)	Proposed EU MRL (mg/kg)
0401060	Rapeseeds/canola seeds	0.02*	N/A

(a) The proposed residue definition for monitoring and risk assessment is parent dimethachlor only.

Table 79: Current EU MRLs for Dimethachlor for Animal Commodities

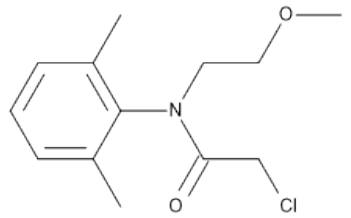
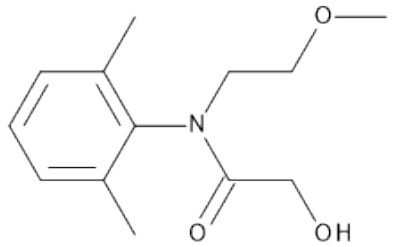
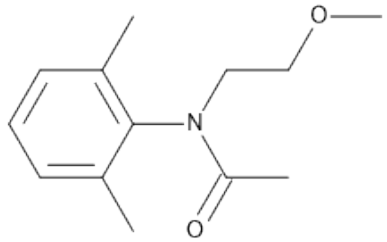
Code	Commodity	Current EU MRL[(a)] (mg/kg)	Calculated MRLs[(b)] (mg/kg)
1011010	Swine muscle	0.01*	0.01*
1011020	Swine fat (free of lean muscle)	0.01*	0.01*
1011030	Swine liver	0.01*	0.01*
1011040	Swine kidney	0.01*	0.01*
1011050	Edible offals (other than liver and kidney)	0.01*	0.01*
1012010	Bovine muscle	0.01*	0.01*
1012020	Bovine fat	0.01*	0.01*
1012030	Bovine liver	0.01*	0.01*
1012040	Bovine kidney	0.01*	0.01*
1012050	Edible offals (other than liver and kidney)	0.01*	0.01*
1013010	Sheep muscle	0.01*	0.01*
1013020	Sheep fat	0.01*	0.01*
1013030	Sheep liver	0.01*	0.01*
1013040	Sheep kidney	0.01*	0.01*
1013050	Edible offals (other than liver and kidney)	0.01*	0.01*
1014010	Goat muscle	0.01*	0.01*
1014020	Goat fat	0.01*	0.01*
1014030	Goat liver	0.01*	0.01*
1014040	Goat kidney	0.01*	0.01*
1014050	Edible offals (other than liver and kidney)	0.01*	0.01*
1015010	Equine muscle	0.01*	0.01*
1015020	Equine fat	0.01*	0.01*
1015030	Equine liver	0.01*	0.01*
1015040	Equine kidney	0.01*	0.01*
1015050	Edible offals (other than liver and kidney)	0.01*	0.01*
1016010	Poultry muscle	0.01*	0.01*
1016020	Poultry fat	0.01*	0.01*
1016030	Poultry liver	0.01*	0.01*
1016040	Poultry kidney	0.01*	0.01*
1016050	Edible offals (other than liver and kidney)	0.01*	0.01*
1020000	Milk	0.01*	0.01*
1030000	Birds' eggs	0.01*	0.01*
1040000	Honey and other apiculture produts	0.05*	0.05*

(a) No residue definition is currently proposed for animal commodities (EFSA 2008).
(b) Calculations from Section CA 7.4
* LOQ values

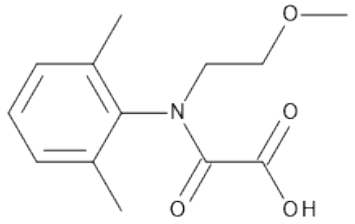
2.7.11 Proposed import tolerances and compliance with existing import tolerances

Not relevant as import tolerances are not included in this EU renewal submission.

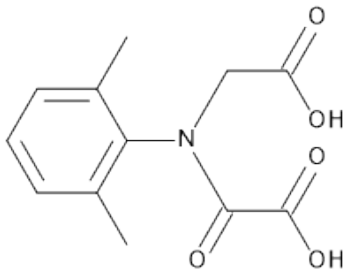
Annex I: Overview of substances and metabolites from residue mestabolism studies

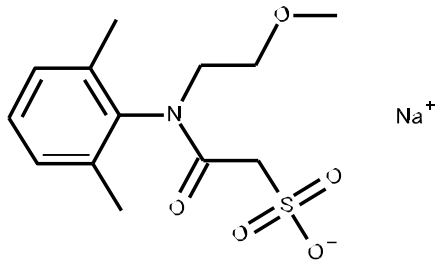
Code Number (Synonyms)	(IUPAC name /SMILES notation /InChiKey)		Compound found in xxx (level): (For each compartment the metabolite is detected in, a separate column should be included; level compound detected to be mentioned in brackets) **			Structural formula
Dimethachlor CGA17020	**Mol. Formula:**	$C_{13}H_{18}ClNO_2$	**Dietary Metabolism Studies:**			
	SMILES	COCCN(C(=O)CCl)c1c(C)cccc1C	**Commodity**	**%TRR**	mg/kg	
	IUPAC Name:	2-Chloro-N-(2,6-dimethyl-phenyl)-N-(2-methoxy-ethyl)-acetamide	N/A			
	InChiKey	SCCDDNKJYDZXMM-UHFFFAOYSA-N				
CGA39981	**Mol. Formula:**	$C_{13}H_{19}NO_3$	**Environmental Fate Studies:**			
	SMILES	COCCN(C(=O)CO)c1c(C)cccc1C	**Substrate**	**%AR**	**DAT**	
	IUPAC Name:	N-(2,6-dimethyl-phenyl)-2-hydroxy-N-(2-methoxy-ethyl) acetamide	Aerobic soil	6.1	120	
	InChiKey	AGEOQFQAZYZFME-UHFFFAOYSA-N	Water sediment	<5% in sediment; <2.3% in water	Various	
			Dietary Metabolism Studies:			
			Commodity	**%TRR**	**mg/kg**	
			Primary Crop			
			OSR stalks	6.4	0.012	
CGA42443 **CSAA031631**	**Mol. Formula:**	$C_{13}H_{19}NO_2$	**Environmental Fate Studies:**			
	SMILES	COCCN(C(=O)C)c1c(C)cccc1C	**Substrate**	**%AR**	**DAT**	
	IUPAC Name:	N-(2,6-dimethyl-phenyl)-N-(2-methoxy-ethyl) acetamide	Anaerobic soil	6.3	37 (7 days aerobic)	
	InChiKey	ZFXDHJUIUORYOX-UHFFFAOYSA-N	Water sediment	10.0 (total system)	112	
			Dietary Metabolism Studies:			
			Commodity	**%TRR**	**mg/kg**	

			CRC#		
			Turnip Leaves (PBI 119)	6.3[a]	0.021[a]
			Turnip Leaves (PBI 30)	3.4[a]	0.054[a]
			Turnip roots (PBI 119)	5.6[a]	0.001[a]
			Turnip roots (PBI 30)	4.4[a]	0.003[a]
			Immature Pak Choi (PBI 30)	7.7[a]	0.043[a]
			Mature Pak Choi (PBI 30)	5.9[a]	0.028[a]
			[a] unresolved from CGA48086		
CGA50266 **CSAA040117**	**Mol. Formula:**	$C_{13}H_{17}NO_4$	**Environmental Fate Studies:**		
	SMILES	COCCN(C(=O)C(=O)O)c1c(C)cccc1C	**Substrate**	**%AR**	**DAT**
	IUPAC Name:	N-(2,6-dimethyl-phenyl)-N-(2-methoxy-ethyl)-oxalamic acid	Aerobic soil	35.5	21
	InChiKey	MHGMSAFPNAKIRZ-UHFFFAOYSA-N	Anaerobic soil	12.39.7	14 (7 days aerobic)
			Water sediment	23.0	63
			Lysimeter	36.2 µg/L	Max in single year
			Dietary Metabolism Studies:		
			Commodity	**%TRR**	**mg/kg**
			Primary Crop		
			OSR pods	20.8	0.033
			OSR stalks	13.6	0.026
			CRC#		
			Barley Forage (PBI 273)	25.6	0.041
			Barley Forage (PBI 30)	24.6	0.112

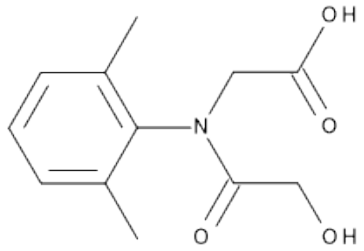
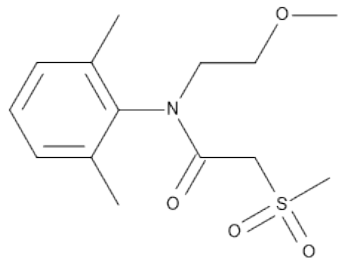


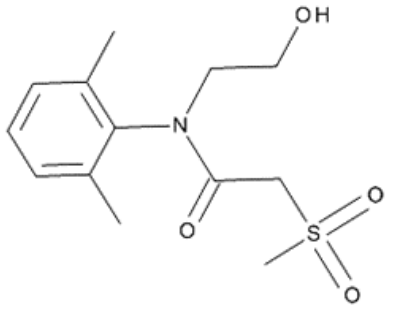
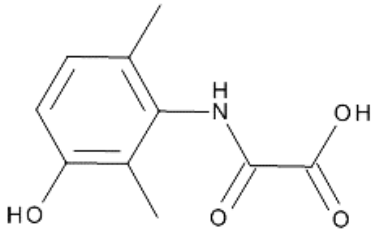
		Barley Hay (PBI 119)	20.7	0.345	
		Barley Hay (PBI 30)	16.6	0.741	
		Barley Grain	7.4	0.007	
		Barley Straw	15.5	0.377	
		Turnip Leaves (PBI 273)	59.2	0.073	
		Turnip Leaves (PBI 30)	30.5	0.478	
		Turnip Roots	55.8	0.015	
		Immature Pak Choi (PBI 273)	53.4	0.054	
		Immature Pak Choi (PB1 30)	36.3	0.201	
		Mature Pak Choi (PBI 273)	64.7	0.029	
		Mature Pak Choi (PBI 30)	39.8	0.188	

CGA102935 **CSAA092578**	**Mol. Formula:**	$C_{12}H_{13}NO_5$	**Environmental Fate Studies:**			
	SMILES	Cc1cccc(C)c1N(CC(=O)O)C(=O)C(=O)O	**Substrate**	**%AR**	**DAT**	
	IUPAC Name:	N-carboxymethyl-N-(2,6-dimethyl-phenyl)-oxalamic acid	Aerobic soil	9.0	63	
	InChiKey	NIHIWXSBMGLAAJ-UHFFFAOYSA-N	Water sediment	2.3 (total system)	182	
			Dietary Metabolism Studies:			
			Commodity	**%TRR**	**mg/kg**	
			CRC[#]			
			Barley Straw (PBI 273)	2.3	0.023	
			Barley Straw (PBI 119)	1.6	0.029	
			Turnip Leaves	1.5	0.024	

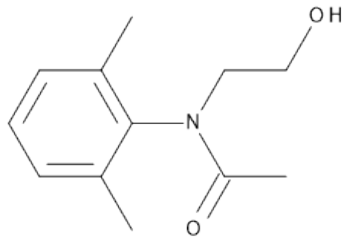
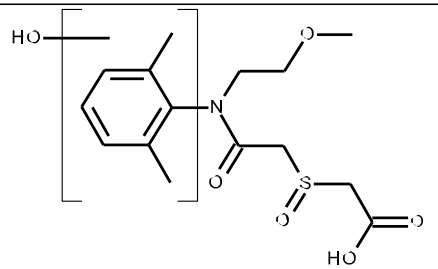
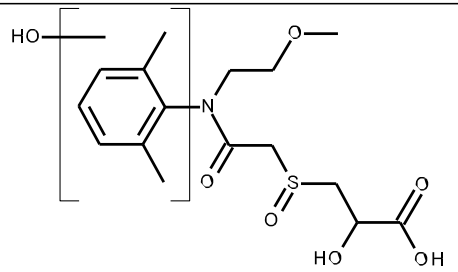
			Turnip Roots	2.5	0.001	
CGA354742 **CSAA438129**	**Mol. Formula:**	$C_{13}H_{18}NO_5S.Na$	**Environmental Fate Studies:**			
	SMILES	[Na+].COCCN(C(=O)CS(=O)(=O)[O-])c1c(C)cccc1C	**Substrate**	**%AR**	**DAT**	
	IUPAC Name:	2-[N-(2-methoxyethyl)-2,6-dimethyl-anilino]-2-oxo-ethanesulfonate sodium salt	Aerobic soil	15.8	14	
	InChiKey	XBBRNOPGXYQVIS-UHFFFAOYSA-M	Anaerobic soil	15.8	14(7 days aerobic)	
			Water sediment	-0	-	
			Lysimeter	35.1 µg/L	Max in single year	
			Dietary Metabolism Studies:			
			Commodity	**%TRR**	**mg/kg**	
			Primary Crop			
			OSR pods	20.8	0.033	
			OSR stalks	13.6	0.026	
			CRC[#]			
			Barley Forage (PBI 273)	25.6	0.041	
			Barley Forage (PBI 30)	24.6	0.112	
			Barley Hay (PBI 119)	20.7	0.345	
			Barley Hay (PBI 30)	16.6	0.741	
			Barley Grain	7.4	0.007	
			Barley Straw	15.5	0.377	
			Turnip Leaves (PBI 273)	59.2	0.073	
			Turnip Leaves (PBI 30)	30.5	0.478	
			Turnip Roots	55.8	0.015	
			Immature Pak Choi (PBI 273)	53.4	0.054	

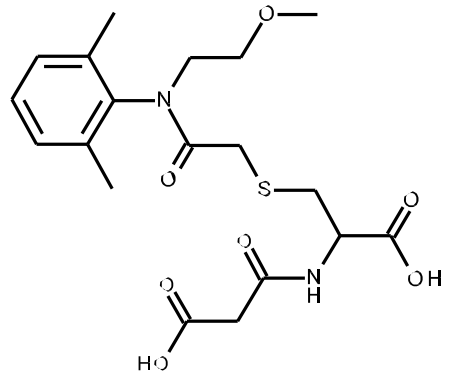
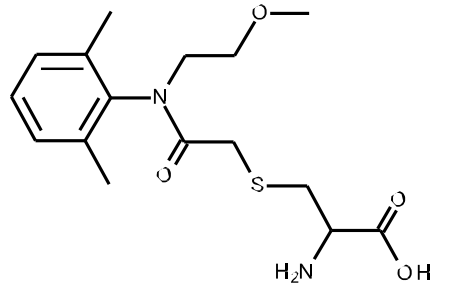
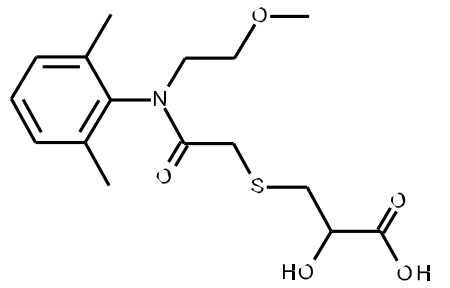
			Immature Pak Choi (PB1 30)	36.3	0.201
			Mature Pak Choi (PBI 273)	64.7	0.029
			Mature Pak Choi (PBI 30)	39.8	0.188
SYN547047 **CSCR604131**	**Mol. Formula:**	$C_{15}H_{21}NO_5S$	**Environmental Fate Studies:**		
	SMILES	COCCN(C(=O)CS(=O)CC(=O)O)c1c(C)cccc1C	**Substrate**	**%AR**	**DAT**
	IUPAC Name:	2-[2-[N-(2-methoxyethyl)-2,6-dimethyl-anilino]-2-oxo-ethyl]sulfinylacetic acid	Aerobic soil	6.8	44
	InChiKey	VAEQAMVGEAIOAB-UHFFFAOYSA-N	Water sediment	-	-
			Lysimeter (incorrectly identified as SYN528702)	11.3 µg/L	Max in single year
			Dietary Metabolism Studies:		
			Commodity	**%TRR**	**mg/kg**
			Primary Crop		
			OSR seed	5.3	0.01
			OSR foliage	6.5	0.45
			CRC[#]		
			Turnip Leaves	6.0	0.093
			Turnip Roots	12.9	0.007
			Mature Pak Choi	3.7	0.017
CGA103699 **CSAA093342** **Met 7U**	**Mol. Formula:**	$C_{12}H_{15}NO_4$	**Environmental Fate Studies:**		
	SMILES	Cc1cccc(C)c1N(CC(=O)O)C(=O)CO	**Substrate**	**%AR**	**DAT**
	IUPAC Name:	2-(N-(2-hydroxyacetyl)-2,6-dimethyl-anilino)acetic acid	Aerobic soil	2.76	7
	InChiKey	XUBMBSRIISONHE-UHFFFAOYSA-N	**Dietary Metabolism Studies:**		
			Primary Crop		
			Commodity	**%TRR**	**mg/kg**
			OSR foliage	4.1	0.282

						
CGA48086 **CSAA037954**	**Mol. Formula:**	$C_{14}H_{21}NO_4S$	**Dietary Metabolism Studies:**			
	SMILES	COCCN(C(=O)CS(=O)(=O)C)c1c(C)cccc1C	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	N-(2,6-dimethylphenyl)-N-(2-methoxyethyl)-2-methylsulfonyl-acetamide	**CRC#**			
	InChiKey	UXKVLBJYEPVNDK-UHFFFAOYSA-N				
			Turnip Leaves (PBI 119)	6.3[a]	0.021[a]	
			Turnip Leaves (PBI 30)	3.4[a]	0.054[a]	
			Turnip roots (PBI 119)	5.6[a]	0.001[a]	
			Turnip roots (PBI 30)	4.4[a]	0.003[a]	
			Immature Pak Choi (PBI 30)	7.7[a]	0.043[a]	
			Mature Pak Choi (PBI 30)	5.9[a]	0.028[a]	
			[a] unresolved from CGA42443			
CGA048090 **CSAA037958** **Met 10U**	**Mol. Formula:**	$C_{13}H_{19}NO_4S$	**Dietary Metabolism Studies:**			
	SMILES	Cc1cccc(C)c1N(CCO)C(=O)CS(=O)(=O)C	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	N-(2,6-dimethylphenyl)-N-(2-hydroxyethyl)-2-methylsulfonyl-acetamide	**CRC#**			
	InChiKey	PRIAKYIWVGVLDU-UHFFFAOYSA-N				

		Barley forage (PBI 273)	3.7	0.006	
		Barley Hay (PBI 119)	2.8	0.047	
		Barley Hay (PBI 273)	3.9	0.031	
		Turnip Leaves (PBI 119)	12.4	0.042	
		Immature Pak Choi (PBI 30)	2.8	0.013	
		Mature Pak Choi (PBI 273)	4.1	0.004	
		In all instances in the CRC CGA048090 detected as the glucose conjugate			
		Rat Metabolism			
		Substrate	**% dose**	**Dose (mg/kg)**	
		Urine	<5.4	100	
SYN551032 **CSDK461821**	**Mol. Formula:**	$C_{10}H_{11}NO_4$	**Dietary Metabolism Studies:**		
	SMILES	Cc1ccc(O)c(C)c1NC(=O)C(=O)O	**Commodity**	**%TRR**	**mg/kg**
	IUPAC Name:	2-(3-hydroxy-2,6-dimethyl-anilino)-2-oxo-acetic acid	**CRC[#]**		
	InChiKey	HWFARDWUDVGBMS-UHFFFAOYSA-N			
		Barley Forage (PBI 273)	17.5	0.041	
		Barley Forage (PBI 30)	13.5	0.061	
		Barley Hay (PBI 273)	18.4	0.146	
		Barley Hay (PBI 30)	10.7	0.475	
		Turnip Leaves (PBI 273)	7.7	0.009	

		Turnip Leaves (PBI 30)	4.8	0.075	
		Turnip roots (PBI 119)	15.6	0.004	
		Immature Pak Choi (PBI 119)	8.1	0.010	
		Immature Pak Choi (PB1 30)	7.9	0.044	
		Mature Pak Choi (PBI 273)	13.4	0.006	
		Mature Pak Choi (PBI 30)	2.8	0.013	
SYN550004	**Mol. Formula:**	$C_{16}H_{23}NO_6S$	**Dietary Metabolism Studies:**		
CSDK367593	**SMILES**	COCCN(C(=O)CS(=O)CC(O)C(=O)O)c1c(C)cccc1C	**Commodity**	**%TRR**	**mg/kg**
	IUPAC Name:	2-hydroxy-3-[2-[N-(2-methoxyethyl)-2,6-dimethyl-anilino]-2-oxo-ethyl]sulfinyl-propanoic acid	**Primary Crop**		
	InChiKey	NLHJQGGTRPRUMI-UHFFFAOYSA-N			
			OSR foliage	46.8	3.261
SYN530561	**Mol. Formula:**	$C_{13}H_{17}NO_5$	**Environmental Fate Studies:**		
CSCC235899	**SMILES**	COCCN(C(=O)CO)c1c(C)cccc1C(=O)O	**Substrate**	**%AR**	**DAT**
	IUPAC Name:	2-[(2-hydroxy-acetyl)-(2-methoxy-ethyl)-amino]-3-methyl-benzoic acid	Lysimeter	2.1 µg/L	Max in single year
	InChiKey	UJKHCLQXFACPDB-UHFFFAOYSA-N			
	Mol. Formula:	$C_{12}H_{17}NO_2$	**Dietary Metabolism Studies:**		
	SMILES	CC(=O)N(CCO)c1c(C)cccc1C	**Commodity**	**%TRR**	**mg/kg**
	IUPAC Name:	N-(2,6-dimethylphenyl)-N-(2-hydroxyethyl) acetamide	**Primary Crop**		
	InChiKey	HWCXVVYBAZSVKZ-UHFFFAOYSA-N			

			Stalks	5.5	-	
			Note: metabolite only produced as a result of treatment with Raney Ni			
U2 **Hydroxylated SYN547047** **No substance code assigned. Proposed structure**	**Mol. Formula:**	$C_{15}H_{21}NO_5S.CH_4O$	**Dietary Metabolism Studies:**			
	SMILES	N/A	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	Hydroxyl-{2-[2-[N-(2-methoxyethyl)-2,6-dimethyl-anilino]-2-oxo-ethyl]sulfinylacetic acid}	**Primary Crop**			
	InChiKey	N/A				
			OSR foliage	6.9	0.482	
U3 **No substance code assigned. Proposed structure**	**Mol. Formula:**	$C_{16}H_{23}NO_6S.CH_4O$	**Dietary Metabolism Studies:**			
	SMILES	N/A	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	Hydroxyl-{2-hydroxy-3-[2-[N-(2-methoxyethyl)-2,6-dimethyl-anilino]-2-oxo-ethyl]sulfinyl-propanoic acid}	**Primary Crop**			
	InChiKey	N/A				
			OSR foliage	6.9	0.482	
U4 **No substance code assigned. Proposed structure**	**Mol. Formula:**	$C_{19}H_{26}N_2O_8S$	**Dietary Metabolism Studies:**			
	SMILES	N/A	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	2-[(2-carboxyacetyl)amino]-3-[2-[N-(2-methoxyethyl)-2,6-dimethyl-anilino]-2-oxo-ethyl]sulfinyl-propanoic acid	**Primary Crop**			
	InChiKey	N/A				
			OSR foliage	8.1	0.564	

						
U5 **No substance code assigned. Proposed structure**	**Mol. Formula:**	$C_{19}H_{26}N_2O_7S$	**Dietary Metabolism Studies:**			
	SMILES	COCCN(C(=O)CSCC(NC(=O)CC(=O)O)C(=O)O)c1c(C)cccc1C	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	2-[(2-carboxyacetyl)amino]-3-[2-[N-(2-methoxyethyl)-2,6-dimethyl-anilino]-2-oxo-ethyl]sulfanyl-propanoic acid	**Primary Crop**			
	InChiKey	HLXPZVJNQAGBFT-UHFFFAOYSA-N				
			OSR foliage	3.7	0.259	
Unknown 6 **No substance code assigned. Proposed structure**	**Mol. Formula:**	$C_{16}H_{23}NO_5S$	**Dietary Metabolism Studies:**			
	SMILES	COCCN(C(=O)CSCC(O)C(=O)O)c1c(C)cccc1C	**Commodity**	**%TRR**	**mg/kg**	
	IUPAC Name:	2-hydroxy-3-[2-[N-(2-methoxyethyl)-2,6-dimethyl-anilino]-2-oxo-ethyl]sulfanyl-propanoic acid	**Primary Crop**			
	InChiKey	HBMZCJRLNABSGK-UHFFFAOYSA-N				
			OSR foliage	-	-	

Annex II: Overview of animal dietary burden calculation

Animal burden calculation — Dimethachlor (AIR4)

According to: "OECD Guidance Document, Series on testing and assessment No 64 and Series on pesticides No 32" and "OECD Guidance Document on Residues in livestock, Series on Pesticides No 73"

Maximum Intake	Cattle						Sheep					
	Beef	500 kg / 12 kg		Dairy	650 kg / 25 kg		Ram/Ewe	75 kg / 2,5 kg		Lamb	40 kg / 1,7 kg	
(mg/kg bw/d)	0,0001	mg/kg bw/d	%	0,0001	mg/kg bw/d	%	0,0001	mg/kg bw/d	%	0,0001	mg/kg bw/d	%
Contributor 1	Rape	meal	20	Canola	meal	10	Rape	meal	15	Rape	meal	15
Contributor 2												
Contributor 3												
Contributor 4												
Median intake	0,0001	mg/kg bw/d		0,0001	mg/kg bw/d		0,0001	mg/kg bw/d		0,0001	mg/kg bw/d	

Maximum Intake	Swine					
	Breeding	260 kg / 6 kg		Finishing	100 kg / 3 kg	
(mg/kg bw/d)	0,0001	mg/kg bw/d	%	0,0001	mg/kg bw/d	%
Contributor 1	Canola	meal	20	Canola	meal	20
Contributor 2						
Contributor 3						
Contributor 4						
Median intake	0,0001	mg/kg bw/d		0,0001	mg/kg bw/d	

Intakes >0.004 mg/kg bw/d are highlighted

Maximum Intake	Poultry								
	Broiler	1,7 kg / 0,12 kg		Layer	1,9 kg / 0,13 kg		Turkey	7 kg / 0,5 kg	
(mg/kg bw/d)	0,0003	mg/kg bw/d	%	0,0002	mg/kg bw/d	%	0,0003	mg/kg bw/d	%
Contributor 1	Canola	meal	18	Canola	meal	10	Canola	meal	20
Contributor 2									
Contributor 3									
Contributor 4									
Median intake	0,0003	mg/kg bw		0,0002	mg/kg bw		0,0003	mg/kg bw	

Intakes expressed on the dry mater basis (mg/kg DM)

mg/kg DM	Cattle		Sheep		Swine	
	Beef	Dairy	Ram/Ewe	Lamb	Breeding	Finishing
Maximum	0,005	0,002	0,003	0,003	0,005	0,005
Median	0,005	0,002	0,003	0,003	0,005	0,005

	Poultry			
	Broiler	Layer	Turkey	Intake >0.1 mg/kg DM in red characters
Maximum	0,004	0,002	0,005	
Median	0,004	0,002	0,005	

Annex III: PRIMo rev. 3.1 Calculations (TMDI)

European Food Safety Authority

EFSA PRIMo revision 3.1; 2019/03/19

Dimethachlor (AIR4)

LOQs (mg/kg) range from:	0.02	to:	0.02
Toxicological reference values			
ADI (mg/kg bw/day):	0.1	ARfD (mg/kg bw):	0.5
Source of ADI:	Dir 09/77	Source of ARfD:	Dir 09/77
Year of evaluation:	2009	Year of evaluation:	2009

Input values

Details - chronic risk assessment

Supplementary results - chronic risk assessment

Details - acute risk assessment/children

Details - acute risk assessment/adults

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

	Calculated exposure (% of ADI)	MS Diet	Expsoure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	Exposure resulting from MRLs set at the LOQ (in % of ADI)	Exposure resulting from commodities not under assessment (in % of ADI)
TMDI/NEDI/IEDI calculation (based on average food consumption)	0.019%	NL toddler	0.02	0.019%	Rapeseeds/canola seeds						0.0%
	0.011%	GEMS/Food G07	0.01	0.011%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.009%	NL child	0.01	0.009%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.007%	GEMS/Food G08	0.01	0.007%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.005%	NL general	0.01	0.005%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.005%	GEMS/Food G10	0.01	0.005%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.004%	GEMS/Food G15	0.00	0.004%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.002%	FI 3 yr	0.00	0.002%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.001%	FI 6 yr	0.00	0.001%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.001%	GEMS/Food G06	0.00	0.001%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.000%	DE general	0.00	0.000%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.000%	DE women 14-50 yr	0.00	0.000%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.000%	DE child	0.00	0.000%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.000%	FR child 3 15 yr	0.00	0.000%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.000%	FR toddler 2 3 yr	0.00	0.000%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.000%	FR adult	0.00	0.000%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.000%	FI adult	0.00	0.000%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.000%	FR infant	0.00	0.000%	Rapeseeds/canola seeds		Grapefruits				0.0%
	0.000%	DK child	0.00	0.000%	Rapeseeds/canola seeds		Grapefruits				0.0%
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				
		ES child			Grapefruits		Grapefruits				

Conclusion:

The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.

The long-term intake of residues of Dimethachlor (AIR4) is unlikely to present a public health concern.

Acute risk assessment /children	Acute risk assessment / adults / general population	Acute risk assessment /children	Acute risk assessment / adults / general population
Details - acute risk assessment /children	Details - acute risk assessment/adults	Hide IESTI new calculations	Show IESTI new calculations

The acute risk assessment is based on the ARfD.
The calculation is based on the large portion of the most critical consumer group.

IESTI new calculations:
The calculation is performed with the MRL and the peeling/processing factor (PF), taking into account the residue in the edible portion and/or the conversion factor for the residue definition (CF). For case 2a, 2b and 3 calculations a variability factor of 3 is used. Since this methodology is not based on internationally agreed principles, the results are considered as indicative only.
Since this methodology is not based on internationally agreed principles, the results are considered as indicative only.

Show results for all crops

Unprocessed commodities

Results for children No. of commodities for which ARfD/ADI is exceeded (IESTI): ---	**Results for adults** No. of commodities for which ARfD/ADI is exceeded (IESTI): ---	**IESTI new Results for children** No. of commodities for which ARfD/ADI is exceeded (IESTI new): ---	**IESTI new Results for adults** No. of commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
0,006%	Rapeseeds/canola	0,02 / 0,02	0,03

IESTI

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
0,00%	Rapeseeds/canola seeds	0,02 / 0,02	0,01

IESTI new

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
0,01%	Rapeseeds/canola	0,02 / 0,02	0,03

IESTI new

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
0,00%	Rapeseeds/canola seeds	0,02 / 0,02	0,01

Expand/collapse list

Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)		**Total number of commodities found exceeding the ARfD/ADI in children and adult diets (IESTI new calculation)**	

Processed commodities

Results for children No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---	**Results for adults** No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---	**Results for children** No of processed commodities for which ARfD/ADI is exceeded (IESTI new): ---	**Results for adults** No of processed commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI

Highest % of ARfD/ADI	Processed commoditi es	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
0,002%	Rapeseeds / oils	0,02 / 0,04	0,01
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!

IESTI

Highest % of ARfD/ADI	Processed commoditie s	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!

IESTI new

Highest % of ARfD/ADI	Processed commoditi es	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
0,00%	Rapeseeds / oils	0,02 / 0,04	0,01
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!

IESTI new

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!

Expand/collapse list

Conclusion:
No exceedance of the toxicological reference value was identified for any unprocessed commodity.
A short term intake of residues of Dimethachlor is unlikely to present a public health risk.
For processed commodities, no exceedance of the ARfD/ADI was identified.

2.8 FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1 Summary of fate and behaviour in soil

Lab studies

Under aerobic laboratory conditions dimethachlor has low persistence in soil (geometric mean DT_{50} of 7.37 days, longest DT_{50} of 18.3 days). Two major soil metabolites, CGA50266 (up to 35.5% of applied radioactivity (AR)) which exhibits low to high persistence and CGA354742 (up to 15.8% AR) which exhibits moderate to high persistence, are formed. Minor metabolites CGA102935 and SYN547047 (formerly known as CGA528702) are also observed. One new aerobic soil metabolism study has been conducted which addresses the identity of minor components (present in the range of 5 - 10% of applied radioactivity that had not been identified in previous studies); CGA102935, SYN530561, CGA369873, CGA103699, CGA37734, CGA373464, CGA16942, CGA39981, CGA39026 and CGA42443.

In summary, under aerobic soil conditions dimethachlor degrades quickly forming eight significant soil metabolites (present at >5% on two occasions or >10% on one occasion or more). Mineralisation of the phenyl ring to carbon dioxide accounted for 13.6 to 43.6% AR after 120 days. The formation of bound residues was a significant pathway, accounting for 33.4 to 56.8 % AR after 120 days.

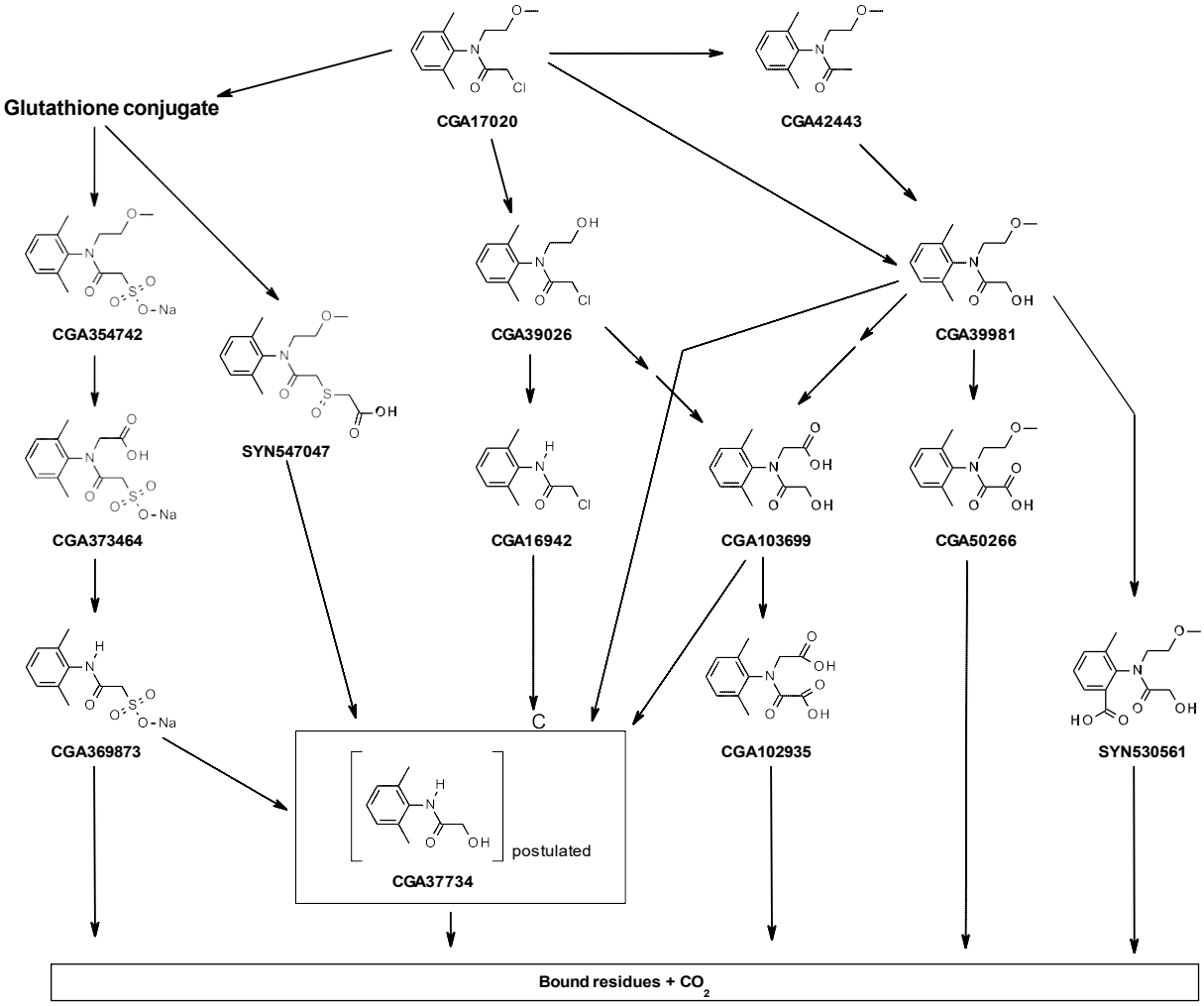


Figure 2.8.1-1: Proposed metabolic pathways of dimethachlor in soil

The soil metabolism of dimethachlor under anaerobic conditions was evaluated during the original Annex I review, *EFSA Scientific Report (2008) 169, 1-111*, based on two anaerobic soil metabolism studies. While one study (Dean, 1995, CGA17020/0355) was accepted for both, aerobic and anaerobic route and rate, concerns were raised over the anaerobic part of the earlier of the two studies (Ellgehausen, 1977, CGA17020/0020). No additional parent-applied studies have been performed. In summary, dimethachlor degrades quickly under anaerobic conditions forming one major metabolite (CGA42443), also seen under aerobic conditions as a minor metabolite (<5%).

The photolytic degradation of dimethachlor when applied to soil was evaluated during the original Annex I review, *EFSA Scientific Report (2008) 169, 1-111*, based on one soil photolysis study (Kirkpatrick, 1995). One additional new soil photolysis study has been performed (Kim-Kang, 2015, CGA017020_50025) as the existing study was not fully guideline compliant study (data provided only on wet soil layer). In summary, the photo-degradation of dimethachlor on soil was slow in dry soil with a degradation half-life ($DegT_{50}$) of 148 days summer sunlight (latitude at 30 - 50°N). Production of photo-degradates was negligible.

Field studies

Field dissipation studies are not triggered by dimethachlor due to its rapid degradation in laboratory soils. However, one small plot radiolabelled study and six new parent applied field dissipation studies have been conducted to understand the behaviour of the metabolites since the worst case DT_{50} values for metabolites CGA42443, CGA50266, CGA354742, CGA369873 and SYN547047 exceeded 60 days.

The radiolabelled study confirmed the rapid degradation of the parent dimethachlor with a DT_{50} of 1.85 days. Three dimethachlor metabolites were detected in this study (CGA50266, CGA354742 and CGA39981). CGA50266, CGA354742 and CGA39981 degraded rapidly to moderate slowly under field conditions with DT_{50} values of 2.71, 68.7 and 94.5 days respectively.

Six new parent-applied field dissipation studies have been conducted in the EU to assess the field degradation of the parent dimethachlor and dimethachlor metabolites in soil. These studies confirms that dimethachlor degrades rapidly under field conditions with DT_{50} values from 7.75 to 41.0 days and all eight dimethachlor metabolites were detected.

Mobility studies

Dimethachlor is slightly mobile with a median K_{OC} value of 68.88 mL/g (29.72 to 128.0 mL/g, n=10). The Freundlich exponent 1/n ranged from 0.76 to 0.95. The findings indicate that the adsorption of dimethachlor to soil is mainly related to interaction with the organic matter fraction. In all studies a Freundlich exponent (1/n) below unity was obtained indicating non-linearity between solution concentration and adsorption. Relative adsorption will thus increase as solution concentration declines. In addition, desorption of dimethachlor was found to be hysteretic, i.e. the adsorption process is not completely reversible, i.e. once adsorbed is far less easily desorbed. There was no evidence of a correlation of adsorption with pH.

The adsorption and desorption behaviour of dimethachlor metabolites CGA42443, CGA50266, CGA354742, CGA369873, CGA373464, SYN530561, SYN547047 and CGA102935 in soil have been evaluated. In all cases the amount adsorbed was very low or negligible with no evidence of a correlation of adsorption with pH.

The behaviour of dimethachlor under lysimeter conditions has been evaluated. The study showed no residues of parent in any leachate sample throughout the 2-year period. Two major metabolites, CGA50266 and CGA354742 were observed in the percolate with maximum yearly mean concentrations of 36.2 and 35.1 µg/L respectively. Four minor metabolites, CGA369873, CGA373464, SYN530561 and SYN547047 (formerly identified as SYN528702) were also observed with maximum yearly mean concentrations of 2.5, 3.3, 2.1 and 11.3 µg/L respectively.

Assessment in relation to the P-criteria

The criteria for persistence in soil, as stated in Annex II to Regulation (EC) 1107/2009, are DT_{50} 120 days (PBT) and 180 days (POP and vPvB). It is assumed that these criteria represent a constant rate of degradation over the decline curve, i.e. that single first order (SFO) kinetics has been assumed implicitly when the criteria were defined.

Based on the longest non-normalised laboratory DT_{50} value in soil, 19.8 days, dimethachlor is clearly below persistence criteria (the initial establishment of a list of CFS).

While no degradation has been observed in the surface water mineralisation study (no half-lives were possible to derive), longest aerobic DT_{50} in fresh water with suspended sediment (aquatic sediment study) is 35 days. Longest aerobic dissipation DT_{50} (whole system) = 44.3 days in water sediment study. This demonstrates that, under conditions that are more environmentally relevant, dimethachlor is not persistent in surface water.

Overall conclusion / persistence in soil

The active substance does not fulfil the persistence criteria (POP / PBT / vPvB / a list of CFS).

2.8.2 Summary of fate and behaviour in water and sediment [equivalent to section 11.1 of the CLH report template]

Hydrolysis and photolysis studies

Dimethachlor and the metabolites CGA50266, CGA354742 and CGA42443 were stable under sterile hydrolysis conditions at 50 °C at pH 1, 4, 5, 7 and 9 and hydrolysis is not considered an important mechanism of degradation for dimethachlor. It was demonstrated that at pH conditions prevalent under natural conditions hydrolysis probably is not a significant route for dimethachlor degradation. Hydrolysis of parent was increased under alkaline conditions (pH 13) but only at high temperature not relevant for environmental conditions. One hydrolysis product, CGA39981 was formed at pH 1 and 13.

Direct photolysis is not expected to be a significant route for degradation of dimethachlor in aqueous solution, since there is no significant overlap between the UV-absorption spectrum of dimethachlor with sunlight. The original Annex I review agreed with this position.

The direct photochemical degradation of dimethachlor metabolites CGA42443, CGA50266 and CGA354742 showed them to be photolytically stable in water under environmentally relevant pH conditions of pH 4, pH 7 and pH 9, and confirming that direct phototransformation of dimethachlor metabolites in the environment is not a relevant degradation process.

Degradation in aquatic systems

The aerobic mineralisation and degradation of dimethachlor in surface water was determined in the laboratory. Dimethachlor remained stable throughout the test therefore degradation in the water phase is considered to be negligible.

The rate and route of degradation of [^{14}C]-dimethachlor has been investigated in four laboratory aerobic and anaerobic water-sediment systems.

The dissipation of dimethachlor from the water sediment systems was moderately fast with the geometric mean $DegT_{50}$ value for dimethachlor in the whole system of 20.2 days (range 8.01 to 44.3 days). The geometric mean DT_{50} for dimethachlor in the water column was 15.7 days (range 6.34 to 34.8 days). The sediment phase was the main degrading phase, and adsorption to sediment was the rate-determining step for the dissipation of dimethachlor from the water phase. In the sediment phase the geometric mean $DegT_{50}$ was 40.2 days.

Metabolites CGA50266 and CGA42443 were the only metabolites detected above 5% in either phase and above 10% in the whole system. CGA42443 was the first metabolite detected in both systems (3 to 7 days after treatment (DAT)) and formed to lower levels than CGA50266 (detected at 7 to 29 DAT). CGA42443 was more evenly distributed between water and sediment phases than CGA50266, which was predominantly present in the water phase. Only trace levels of CGA50266 were found in the sediment phases in both systems.

Additional minor metabolites (none exceeding 7.3% AR) were identified as CGA102935, CGA39981, CGA16942 and CGA39026. Mineralisation was a minor route of degradation with CO_2 accounting for 2.6 to 3.5 % AR. Formation of bound residues was a major pathway of disappearance of dimethachlor and its metabolites with 40 to 60% AR over the course of the study. Organic matter fractionation of the bound residues in two water sediment systems showed ^{14}C associated mainly with the humin fraction (up to 46.2%) and to a lesser extent with the humic acid (<3.5%) and fulvic acid fractions (up to 13.3%).

2.8.2.1 Rapid degradability of organic substances

Relevant studies on degradation of dimethachlor are listed in the table below. These studies show that dimethachlor is not readily biodegradable and not rapidly degraded by hydrolysis or photolysis in the aquatic environment. In surface water simulations there was no evidence of significant degradation of dimethachlor. In aquatic sediments, dimethachlor is rapidly dissipated from the water and the presence of high amounts of non-extractable radioactivity in sediment suggests that formation of strongly bound residues was a major pathway for the disappearance of dimethachlor and its degradates from aquatic systems. Dimethachlor is not considered to be rapidly degradable for the purposes of classification and labelling.

Table 80: Summary of relevant information on rapid degradability

Method	Results*	Key or Supportive study	Remarks	Reference
Ready biodegradability. 29 days, 22 ± 2°C Dimethachlor (96.8%	0% of the theoretical value of dimethachlor within	The study is acceptable.	The reference substance was degraded to 80% within a 10-day time	Weinstock (1994)

purity), 29.1 and 30.3 mg/L. OECD 301/B. GLP.	29 days. Not readily biodegradable.	Key study.	window. Dimethachlor did not impair the degradation of the reference compound.	
Hydrolysis. Incubation temperatures were 30°C; 50°C, and 70°C for pH 1, 5, 7 and 9 and 5°C, 30°C and 50°C for pH 13. Dimethachlor at a concentration of 100 mg a.s./L was investigated. Non-guideline study carried out prior to the implementation of GLP.	Hydrolytic half life of dimethachlor at 20°C was >200 days at pH 1, 5, 7 and 9 and 9.3 days at pH 13.	The study is acceptable. Key study.	Degradation observed but no attempts were made to identify degradates. One hydrolysis product (CGA39981) was formed at pH 1 and 13.	Burkhard (1974)
Hydrolysis. Sterile aqueous solutions buffered to pH values of 1, 5, 7 or 9 and incubated at a temperature of ca 50°C or 20°C in the dark for up to 30 days. Phenyl-U-^{14}C labelled dimethachlor (radiochemical purity: >99%) at 5 mg ai/L. OECD 111, BBA Pamphlet NO 55, Part I GLP.	Dimethachlor is hydrolytically stable in aqueous solution buffered to pH values of 1, 5, 7 or 9 and stored in darkness for up to 30 days at 20°C or 5 days at 50°C.	The study is acceptable. Key study.	No decline in dimethachlor could be observed during the experiment and, therefore, no degradation half-lives can be calculated.	Kirkpatrick (1995a)
Surface water simulation. Aerobic conditions in the dark at 20 ± 2 °C for up to 62 days. Sterile controls were maintained under the same conditions for up to 87 days. Application rates of 10 and 95 µg/L ^{14}C-dimethachlor (radiochemical purity: >99%). Regulation (EU) 283/2013, OECD 309. GLP.	The parent compound remained stable throughout the test. Mean levels of parent were at 102.6 and 102.5% AR at the end of the incubation period (62 DAT) for the low and high test concentrations, respectively.	The study is acceptable. Key study.	The degradation of sodium ^{14}C- benzoate to ^{14}C- carbon dioxide indicated a viable microbial population was established (average 89.6 and 91.2 % AR at 14 and 21 days after treatment (DAT), respectively). No significant degradation of ^{14}C- dimethachlor was observed under the test conditions; therefore, DegT50 values could not be determined.	McLaughlin (2015)
Pond dissipation. Dimethachlor formulated as EC 400 (Teridox®) was applied with a motor sprayer to the surface of a pond which aimed to reach a concentration of 1 mg ai/L of dimethachlor in the pond water. Samples were collected over 63 days and subsequently water and sediment samples were extracted and analysed. Non-guideline study carried out prior to the implementation of GLP.	The parent compound disappeared with a half-life of approximately 7 days, reaching a water residue level of 0.03 mg a.s./L 63 days following application. Residues in the sediment were ≤0.02 mg a.s./kg (limit of detection) over the whole test period.	The study is acceptable. Key study.	Dimethachlor dissipated from the water but the mechanism was not studied.	Keller (1976)

Degradation and metabolism in aquatic systems. Nominal rate of 0.497 mg a.s./L (corresponding to an application rate of 1500 g a.s./ha assuming a uniform distribution of dimethachlor in a 30 cm water layer), radiochemical purity: >99.2%; incubated for up to 182 days at 20 ± 1°C, in the dark. BBA IV: 5-1, Dutch Registration Guideline, Section G.2, EPA 540/9-82-021, Section 162-4. GLP.	The presence of high amounts of non-extractable radioactivity at the end of the study (river: 56.7%, pond: 50.9%) suggests that formation of strongly bound residues was a major pathway for the disappearance of ^{14}C- dimethachlor and its degradates from the aquatic systems. The major metabolites formed in water and sediment were tentatively characterised by co-chromatography to be CGA50266 and CGA42443. The maximum amount of CGA50266 was 13.8% (river) and 16.0% (pond) after 112 days. CGA42443 occurred at maximum levels of 8.2% (river, 28 days) and 10.1% (pond, 112 days). Rates of dissipation of dimethachlor from the total systems and from the water phases were calculated by applying a first order two compartment model and non-linear regression analysis. The total system DT_{50} values were 9 days (River) and 23 days (Pond) and the water phase DT_{50} values were 6 days (River) and 16 days (Pond).	The study is acceptable. Key study.	The total radioactivity recovered at all time intervals averaged 98.9 ±2.1% AR for the river and 98.6 ±2.4% AR for the pond system. All volatile radioactivity was characterised as CO_2 reaching a maximum of 3.5% (river) and 3.1% (pond) AR on day 182, indicating little mineralisation. DT_{50} values for dimethachlor in water and total system were re-calculated from the original report data using first order kinetics in one compartment. In addition, times of dissipation were calculated also for the sediment phase. Similar DT_{50} values were calculated for the total system and water phase. The sediment dissipation DT_{50} values were 1.5 days (River) and 16 days (Pond). The identity of both CGA50266 and CGA42443 was confirmed by LC/MS.	Flückiger (1995) and Flückiger and Sägesser (1995)
Aerobic Aquatic-Sediment Metabolism. Nominal rate of 0.33 µg/mL (based on the maximum single	For the water phase, parent dimethachlor dissipation DT_{50} values were 17 days and 35 days for the	The study is acceptable. Key study.	The mean mass balance from all aerobic water/sediment systems was 102.6% AR (range 92.2 to 107.6% AR).	Connor (2016b)

application rate of 1000 g a.s./ha), radiochemical purity: 99.2%, maintained in dark conditions at 20 ± 2 °C for 99 days. OECD 308, U.S. EPA OCSPP 835.4300, Regulation (EC) No. 1107/2009. GLP.	Taunton River and Weweantic River Systems, respectively. The total system degradation half-lives for parent dimethachlor using simple first order (SFO) kinetics were 22 and 45 days for the Taunton River and Weweantic River Systems, respectively.		Mineralization was a minor route of degradation, CO_2 accounted for 3.0% to 3.2% AR for the Weweantic River and Taunton River systems. The other volatile organic compounds accounted for ≤ 0.1% AR in both test systems. No volatile radioactivity (<1.0%) was observed in the aerobic systems.	
Direct phototransformation of dimethachlor in water. UV/VIS-spectra were measured in dilute phosphate buffer of pH 7.4. Rate constants k_a and half-lives $t_{1/2}$ for direct photolysis in surface water for 40°N and 50°N in summer were calculated with the program GCSOLAR. OECD Proposal for a New Guideline, August 2000; OECD Environmental Health and Safety Publications, Series on Testing and Assessment, No. 7; OPPTS 835.2210; Zepp & Cline (1977); OECD 101; OPPTS 830.7050. GLP.	The decadic molar absorption coefficients are far below the trigger value of ε = 10 at wavelengths >290nm.	The study is acceptable. Key study.	The spectral data clearly indicate that direct photolysis is not considered to be a relevant process for the fate of dimethachlor in the environment.	Schmidt (2001)
Photolysis of [U-^{14}C-phenyl] dimethachlor (radiochemical purity: >99%) in aqueous solution under laboratory conditions. Sterile aqueous buffer solutions at pH 7, concentration of 5 mg/L, continuously irradiated with xenon arc light for up to 15 days. Irradiated and dark control solutions were maintained at 25°C. Samples were analysed for radioactivity recovery and for relative proportions of dimethachlor and	In irradiated and dark control solutions dimethachlor was not significantly degraded. Throughout the whole study period of 15 days, the test substance accounted for between 96.6% - 98.3% (irradiated solutions) and 97.0% - 98.8% (dark control solutions) of test solution radioactivity, respectively. Photolysis is not	The study is acceptable. Key study.	Recoveries of total radioactivity from test solutions were in the range 96.1 -100.2% of the applied radioactivity at all times. There was no detectable formation of volatile radioactivity or photoproducts of dimethachlor during irradiation equivalent to 39 days of natural sunlight at latitude 40°N.	Kirkpatrick (1995b)

potential photodegradation products by HPLC and 2D TLC. Volatile radioactivity was collected with several trapping agents. USA EPA Subdivision N, 161-2. GLP.	likely to be a significant route of degradation of dimethachlor under these conditions.			
Adsorption and desorption in various soil types. 5 different soils using the batch equilibrium method, ^{14}C labelled dimethachlor prepared at five concentrations of 1.25, 2.5, 5.0, 10.0 and 20.0 mg a.s./L. The solutions (100 mL aliquots) were added to soil (10 to 50 g dry weight) and allowed to equilibrate while shaking for 24 hours at 20°C in sealed centrifuge tubes. After equilibration the phases were separated by centrifugation. Dimethachlor concentrations in aqueous phases were determined directly by liquid scintillation counting (LSC). The wet soil pellets remaining after adsorption were desorbed twice. This is a non-guideline study, carried out prior to the implementation of GLP.	The Freundlich adsorption coefficient K_F varied between 0.46 mL/g for the Collombey loamy sand and 18.4 mL/g for the Illarzaz silt loam. The slopes (1/n) of the adsorption isotherms ranging from 0.90 to 0.95 with correlation coefficients >0.99 indicate that the experimental data were adequately described by the non linear Freundlich equation. The adsorption constants normalised for the organic carbon content (K_{OC}) ranged from 56.65 to 128 mL/g with an average K_{OC} value of 77.85 mL/g.	The study is acceptable. Key study.	Dimethachlor has a moderate adsorption capacity to most soils. The results for desorption are presented as percent of the amount adsorbed. The sum of the percentage released in two desorption steps ranged from 41.8 to 73.1% indicating that adsorption was not a fully reversible process.	Keller (1984).
Adsorption and desorption in 5 soil types. Adsorption/desorption of ^{14}C- dimethachlor (radiochemical purity: >99%), prepared in 0.01M calcium chloride at four concentrations of 0.1, 0.5, 1.0 and 2.5 mg a.s./L. After 22 hours of agitation at 20°C in the dark, the phases were separated by centrifugation. Dimethachlor concentrations in aqueous phases were determined directly by LSC. The wet	The Freundlich adsorption coefficient K_F varied between 0.32 mL/g for the Speyer sand and 13.3 mL/g for the Illarzaz silt loam. The slopes (1/n) of the adsorption isotherms ranging from 0.76 to 0.94 with correlation coefficients >0.99 indicate that the experimental data were adequately described by the	The study is acceptable. Key study.	Dimethachlor is a compound with a moderate adsorption capacity to most soils. The desorption K_{OC} values from the soils were somewhat higher than the adsorption values ranging from 42 to 133 and 33 to 196 mL/g for the 1st and 2nd desorption step, respectively. This might indicate that adsorption was not fully reversible. A mean K_{OC} of 62.51 would classify dimethachlor as slightly mobile in soil.	Burgener (1995)

soil pellets remaining after adsorption were desorbed twice. OECD 106; US EPA Subdivision N, Section 163 – 1; Environmental Chemistry and Fate, Guidelines for Registration of Pesticides in Canada. GLP.	Freundlich equation. The adsorption constants normalised for the organic carbon content (K_{OC}) ranged from 29.72 to 95.37 mL/g with an average K_{OC} value of 62.51 mL/g.			

** data on full mineralization should be reported*

2.8.2.1.1 Ready biodegradability

One study investigating the ready biodegradability of dimethachlor is available (Weinstock, 1994). It concluded that dimethachlor is classified as "not readily biodegradable".

Study 1 Weinstock (1994)

The test was performed with dimethachlor technical grade (Batch No. OP.110001; 96.8% purity; carbon content 61.05%) in a mineral medium inoculated with activated sludge collected from a sewage treatment plant. Concentrations of 29.1 and 30.3 mg dimethachlor, corresponding to 17.8 and 18.5 mg theoretical organic carbon (ThOC)/L were tested. During incubation the evolved carbon dioxide was measured at 0, 3, 7, 10, 13, 17, 20, 24, 28 and 29 days. The percentage of degraded test substance was calculated by comparing the quantities of inorganic carbon (CO_2) measured in the absorber flasks at the respective sampling intervals with the theoretical carbon content.

There was no biodegradation (0% of the theoretical value) of dimethachlor within 29 days. The reference substance was degraded to 80% within a 10-day time window. Dimethachlor did not impair the degradation of the reference compound.

Dimethachlor is classified as "not readily biodegradable" (Annex VI of Directive 67/548/EEC).

2.8.2.1.2 BOD5/COD

No relevant studies.

2.8.2.2 Other convincing scientific evidence

2.8.2.2.1 Aquatic simulation tests

Four relevant simulation studies are available on the degradation of dimethachlor in water and water-sediment systems. In a surface water simulation, McLaughlin (2015) showed that no significant degradation was observed under the test conditions; therefore, DegT50 values could not be determined.

Keller (1976) studied the dissipation of dimethachlor in pond water. This was a non-guideline study with limitations in design and/or reporting but otherwise adequate for assessment. The study was carried out prior to the implementation of GLP. The results showed that dimethachlor disappeared from the water with a half-life of approximately 7 days, reaching a residue level of 0.03 mg a.s./L 63 days following application. Residues in the sediment were ≤0.02 mg a.s./kg (limit of detection) over the whole test period.

In the third study (reported in 2 reports: Flückiger (1995) and Flückiger and Sägesser (1995)) the fate of ^{14}C-dimethachlor was studied in a water-sediment simulation conducted to GLP. Rates of dissipation of dimethachlor from the total systems and from the water phases were calculated by applying a first order two compartment model and non-linear regression analysis. The total system DT_{50} values were 9 days (River) and 23 days (Pond) and the water phase DT_{50} values were 6 days (River) and 16 days (Pond).

DT_{50} values for dimethachlor in water and total system were re-calculated from the original report data using first order kinetics in one compartment. In addition, times of dissipation were calculated also for the sediment phase. Similar DT_{50} values were calculated for the total system and water phase. The sediment dissipation DT_{50} values were 1.5 days (River) and 16 days (Pond).

In the fourth study, Connor (2016) conducted a GLP study to investigate the rate and route of degradation of ^{14}C-phenyl ring labelled dimethachlor in two different water sediment systems. Dissipation of dimethachlor from the water phase of Taunton River water-sediment test system was relatively fast, with the parent compound representing only 0.4% (averaged) of the applied radioactivity (AR) after 99 days of incubation. Dissipation of dimethachlor from the water phase of Weweantic River water-sediment test system was slower, with the parent compound representing 15.0% (averaged) of the applied radioactivity after 99 days of incubation.

The dissipation and degradation rates were calculated using non-linear regression and first-order kinetics (SFO). For the water phase, parent dimethachlor dissipation DT_{50} values were 17 days and 35 days for the Taunton River and Weweantic River Systems, respectively. The total system degradation half-lives for parent dimethachlor using simple first order (SFO) kinetics were 22 and 45 days for the Taunton River and Weweantic River Systems, respectively.

Study 1 McLaughlin (2015)

The extent of mineralization and the rate and route of degradation of [^{14}C]-dimethachlor were investigated in a natural water test system collected from White's Pond, Plymouth MA. [^{14}C]- dimethachlor was applied to the water at nominal rates of 10 and 95 µg/L (low and high doses, respectively). The 95 µg/L rate was also applied to sterilized test system (natural water). The systems were incubated under aerobic conditions and maintained in dark conditions at 20 ± 2 °C for up to 62 days. The sterile controls were maintained under the same conditions for up to 87 days. For each system, duplicate samples were taken for analysis at up to seven intervals.

At each sampling time, the quantity of radioactivity in the water was determined by liquid scintillation counting (LSC). Samples were centrifuged to precipitate any solids prior to high performance liquid chromatography with radiochemical detection (HPLC/RAM) analysis. Any volatile radioactivity was continuously flushed from the vessels, collected in traps and analysed. A mass balance was determined for each sample.

Separate reference samples (treated with sodium ^{14}C-benzoate at 10 µg/L) of natural water were prepared to determine whether a viable microbial population was present in the test system.

Separate blank control samples were similarly incubated to allow water quality measurements at each sampling interval.

The mean mass balance for the low and high test concentration natural water samples were 101.7 and 102.4% of applied radioactivity (AR) with ranges of 95.1 to 108.4% and 100.1 to 106.4%, respectively. The mass balances for the sterilized incubation groups were 101.2 and 97.5% AR for the water dosed at the high concentration.

The parent compound remained stable throughout the test (mean levels of parent were at 102.6 and 102.5% AR remained at the end of the incubation period (62 DAT) for the low and high test concentrations, respectively), therefore resultant DegT50 values cannot be estimated. ^{14}C- dimethachlor was found to be stable in the sterilized samples as well (mean levels of 99.3% AR (98.7% as parent) remained at 87 DAT).

Small amounts of ^{14}C- dimethachlor mineralized to $^{14}CO_2$ (0.8 and 1.3 % AR observed in the low and high test concentrations, respectively).

The degradation of sodium ^{14}C-benzoate to ^{14}C- carbon dioxide indicated a viable microbial population was established (average 89.6 and 91.2 % AR at 14 and 21 days after treatment (DAT), respectively).

No significant degradation was observed under the test conditions; therefore, DegT50 values for dimethachlor could not be determined.

Study 2 Keller (1976)

Dimethachlor formulated as EC 400 (Teridox®) was applied with a motor sprayer to the surface of a pond near Les Evouettes, VS, Switzerland in June 1974. The pond had a surface area of 185 m^2, a mean depth of 1 m and a total volume of about 185 m^3. The rate of application had aimed to reach a concentration of 1 mg ai/L of dimethachlor in the pond water. At time intervals of 1 and 5 hours, and 3, 7, 14, 30, 45 and to 63 days after treatment, ten 3L-water samples and ten 3kg-bottom sediment samples were taken, pooled and 1 L and 1 kg sub-samples, respectively, were retained for analysis. The sub-samples were stored at -20°C until extraction and analysis for dimethachlor using gas chromatography (GC) with alkali flame ionisation detection.

The limit of detection for dimethachlor was 0.01 mg a.s./L in water and 0.02 mg a.s./kg in sediment. The recovery of the method was between 88 and 92% for water (0.1-1.0 mg a.s./L) and between 90 and 92% for sediment (0.1-1.0 mg a.s./kg). Residues of dimethachlor in water declined from 1.53 mg a.s./L one hour after treatment to 0.03 mg a.s./L after 63 days. The high residue value, 1 hour after application, which is clearly above the anticipated initial concentration in water, does probably not reflect the actual concentration but can more likely be related to the non-homogeneous distribution of the test compound in the water body. In the sediment, residue levels were below the limit

of detection except in the period between days 3 and 14 after treatment when residues between 0.02 and 0.03 mg a.s./kg were found.

Dimethachlor (Teridox®) sprayed onto pond water at a concentration of 1 mg a.s./L in the pond water disappeared with a half-life of approximately 7 days, reaching a residue level of 0.03 mg a.s./L 63 days following application. Residues in the sediment were ≤0.02 mg a.s./kg (limit of detection) over the whole test period.

Study 3 Flückiger (1995) and Flückiger and Sägesser (1995)

The distribution, degradation and metabolism of phenyl-U-^{14}C labelled dimethachlor (radiochemical purity: >99.2%) were investigated in equilibrated water-sediment systems. Water and sediment specimens from natural sources in Switzerland.

After a 4 week equilibration period, the phenyl-U-^{14}C labelled test substance was applied to the water surface at a target concentration of 0.497 mg a.s./L, corresponding to an application rate of 1500 g a.s./ha assuming a uniform distribution of dimethachlor in a 30 cm water layer. The test systems were incubated for up to 182 days at 20 ± 1°C, in the dark. At appropriate sample intervals the water and sediments were separated, extracted and analysed.

The total radioactivity recovered at all time intervals averaged 98.9 ±2.1% AR for the river and 98.6 ±2.4% AR for the pond system. All volatile radioactivity was characterised as $^{14}CO_2$ reaching a maximum of 3.5% (river) and 3.1% (pond) AR on day 182, indicating little mineralisation.

At the end of the study period (day 182), dimethachlor had nearly completely disappeared in both systems: in the water phases it was below limit of quantification (0.1% AR equivalent to 0.001 mg a.s./L) and also in the sediments only traces of 0.1% (river) and 0.3% (pond) AR were recovered.

Degradation of the parent molecule resulted in the formation of at least 11 fractions in the aquatic systems (water and sediment). The two major fractions were identified as the oxalic acid derivative CGA50266 and the dechlorination product CGA42443. CGA50266 reached a maximum of 10.1% AR in the water and 3.7% AR in the sediment after 112 days in the river system and of 13.0% AR (182 days) in the water and 4.2% AR in the sediment (day 112) in the pond system. The levels of CGA42443 reached peak concentrations in the river system of 4.4% AR in the water after 21 days and 4.3% AR in the sediment after 7 days, whilst in the pond system maximum of 5.5% AR in the water and 4.5% AR in the sediment were found after 112 days. The early occurrence of CGA42443 in the sediments indicates dehalogenation of dimethachlor under reducing conditions of the anaerobic environment.

The identity of both CGA50266 and CGA42443 was confirmed by LC/MS (Flückiger & Sägesser, 1995). In addition to the two major metabolites at least nine minor fractions were found. None of them exceeded the total level of 7.3% AR in water phase and sediment of the river and the pond system at any time interval. Four of these minor metabolites were characterized by co-chromatography with reference standard compounds as CGA102935, CGA39981, CGA16942 and CGA39026.

The presence of high amounts of non-extractable radioactivity at the end of the study (river: 56.7%, pond: 50.9%) suggests that formation of strongly bound residues was a major pathway for the disappearance of ^{14}C- dimethachlor and its degradates from the aquatic systems.

The major metabolites formed in water and sediment were tentatively characterised by co-chromatography to be CGA50266 and CGA42443. The maximum amount of CGA50266 was 13.8% (river) and 16.0% (pond) after 112 days. CGA42443 occurred at maximum levels of 8.2% (river, 28 days) and 10.1% (pond, 112 days). Besides these metabolites, numerous minor degradates were found, none of which exceeded 7.3% of the applied radioactivity during the study.

The metabolite patterns were very similar in the river and the pond system. The early occurrence of CGA42443 in the sediments suggests that CGA17020 is dehalogenated to CGA42443 under reducing conditions in the anaerobic layer of the sediment.

Rates of dissipation of dimethachlor from the total systems and from the water phases were calculated by applying a first order two compartment model and non-linear regression analysis. The total system DT_{50} values were 9 days (River) and 23 days (Pond) and the water phase DT_{50} values were 6 days (River) and 16 days (Pond).

DT_{50} values for dimethachlor in water and total system were re-calculated from the original report data using first order kinetics in one compartment. In addition, times of dissipation were calculated also for the sediment phase. Similar DT_{50} values were calculated for the total system and water phase. The sediment dissipation DT_{50} values were 1.5 days (River) and 16 days (Pond).

Study 4 Connor (2016)

The rate and route of degradation of ^{14}C-phenyl ring labelled dimethachlor was investigated in two different water sediment systems: Taunton River (sandy loam) and Weweantic River (sand). ^{14}C-labeled dimethachlor was applied to

the water at a nominal rate of 0.33 µg/mL (based on the maximum single application rate of 1000 g a.s./ha) in the water phase. Both sediment types were maintained under aerobic conditions. The systems were incubated in the laboratory and maintained in dark conditions at 20 ± 2 °C for 99 days. Water and sediment samples from each system were analysed at 0, 1, 3, 6, 14, 29, 63 and 99 days after treatment (DAT).

The mean mass balance from all aerobic water/sediment systems was 102.6% applied radioactivity (AR) (range 92.2 to 107.6% AR).

Dissipation of dimethachlor from the water phase of Taunton River water-sediment test system was relatively fast, with the parent compound representing only 0.4% (averaged) of the AR after 99 days of incubation. Dissipation of dimethachlor from the water phase of Weweantic River water-sediment test system was slower, with the parent compound representing 15.0% (averaged) of the applied radioactivity after 99 days of incubation.

The dissipation and degradation rates were calculated using non-linear regression and first-order kinetics (SFO). For the water phase, parent dimethachlor dissipation DT_{50} values were 17 days and 35 days for the Taunton River and Weweantic River Systems, respectively. The total system degradation half-lives for parent dimethachlor using simple first order (SFO) kinetics were 22 and 45 days for the Taunton River and Weweantic River Systems, respectively.

Under aerobic conditions, the major degradates of dimethachlor were found to be CGA50266 and CGA42443. CGA50266 reached maximum values of 4.6% and 1.2% AR after 63 and 99 days in the Taunton River and Weweantic River sediment phases, respectively. CGA42443 reached maximum values of 4.3% and 2.5% AR at 99 DAT in the Taunton River and Weweantic River sediment phase, respectively. CGA50266 reached maximum values of 18.4% and 9.7% AR at 63 and 99 DAT for the Taunton River and Weweantic River water phase, respectively. CGA42443 reached maximum values of 5.5% and 3.5% AR at 29 DAT for the Taunton River and Weweantic River water phase, respectively. Several minor degradates were observed in the water and sediment phases for both the Taunton River and Weweantic River test systems, however, these individual peaks were each observed to be < 5% AR and were not considered any further.

Mineralization was a minor route of degradation, CO_2 accounted for 3.0% to 3.2% AR for the Weweantic River and Taunton River systems. The other volatile organic compounds accounted for ≤ 0.1% AR in both test systems. No volatile radioactivity (<1.0%) was observed in the aerobic systems.

Organic matter fractionation of bound residues during the aerobic phase demonstrated ^{14}C was mainly associated with the humin fraction, representing 46.2% AR for the Taunton River system and 40.1% AR for the Weweantic River system. In both systems, the majority of the remainder was associated with the fulvic acid fraction.

2.8.2.2.2 Field investigations and monitoring data (if relevant for C&L)

No relevant data.

2.8.2.2.3 Inherent and enhanced ready biodegradability tests

No relevant data.

2.8.2.2.4 Soil and sediment degradation data

Please refer to 2.8.1 for soil degradation and to 2.8.2.2.1 for sediment degradation (water/ sediment systems).

2.8.2.2.5 Hydrolysis

Two hydrolysis studies are available. The first (Burkhard, 1974) was a non-guideline study with limitations in design and/or reporting but otherwise adequate for assessment. It was carried out prior to the implementation of GLP and, therefore, no claim is made as to its GLP compliance. The second study (Kirkpatrick, 1995a) was conducted in accordance with OECD 111 test guideline and was performed to GLP. Both studies suggest that hydrolysis is unlikely to be a significant degradation mechanism for dimethachlor in the aquatic environment.

Study 1 Burkhard (1974)

The hydrolytic stability of dimethachlor at a concentration of 100 mg a.s./L was investigated in 0.1N HCl (pH 1), 0.1N NaOH (pH 13) and in aqueous buffer solutions with pH-values ranging from 5 to 9. Incubation temperatures were 30°C; 50°C and 70°C for pH 1, 5, 7 and 9 and 5°C, 30°C and 50°C for pH 13. Aliquots of the test solutions were taken up to 28 days and were extracted with n-hexane. Concentration of dimethachlor in the extracts was determined

using GC equipped with alkali flame ionisation detection. For identification of hydrolysis products additional experiments were conducted with phenyl-U-^{14}C labelled dimethachlor (0.69 MBq/mg) at pH 1 and 13. n-hexane extracts were analysed by radio-TLC and specific spots also by GC/MS. From the rate constants Arrhenius parameters for each pH value were calculated.

Hydrolysis could be adequately described by first order kinetics. Based on the rate constants, Arrhenius parameters for each pH-value were calculated and used for the determination of the hydrolytic half-life at 20°C. The half-life was >200 days at pH 1, 5, 7 and 9 and 9.3 days at pH 13. One hydrolysis product was formed at pH 1 and 13 and was identified as 2,6-dimethyl-N-(methoxyethyl)-hydroxyacetanilide (CGA39981).

Under acidic and basic conditions, a direct degradation of dimethachlor to 2,6-dimethyl-N-(methoxyethyl)-hydroxyacetanilide (CGA39981) takes place.

The rate constant determinations demonstrate that dimethachlor is rather stable at pH-values ranging from 1 to 9, whereas at pH 13 the compound is readily hydrolysed with a calculated half-life of 9.3 days at 20°C. The half-lives for the other pH levels were determined to be >200 days at 20°C.

Study 2 Kirkpatrick (1995a)

The hydrolytic stability of dimethachlor, 2-chloro-N-(2,6-dimethylpheny1)-N-(2-methoxyethyl) acetamide, was studied in sterile aqueous solutions buffered to pH values of 1, 5, 7 or 9 and incubated at a temperature of ca 50°C or 20°C in the dark. Phenyl-U-^{14}C labelled dimethachlor (Batch No.: CFQ-7176-2; radiochemical purity: >99%; specific radioactivity: 2.57 MBq/mg) was added to the buffers at a concentration of 5 mg a.s./L. A pre-test was run for five days at 50°C. The main test was performed at 20°C with duplicate samples taken at 0, 5, 10, 14, 18, 22, 26, and 30 days. The test solutions were analysed for dimethachlor and its hydrolysis products by TLC and HPLC.

Sterility was maintained for the duration of the study. Total recoveries of the applied radioactivity were in the range of 98 - 103%. At all pH values dimethachlor was hydrolytically stable. Dimethachlor represented between 95.1% and 97.7% of the solution radioactivity at all times studied. The data show that dimethachlor is hydrolytically stable in aqueous solution buffered to pH values of 1, 5, 7 or 9 incubated for up to 30 days at 20°C or 5 days at 50°C. As a result of the stability of dimethachlor, no degradation half-lives could be calculated.

The results of this study show that dimethachlor is hydrolytically stable in aqueous solution buffered to pH values of 1, 5, 7 or 9 and stored in darkness for up to 30 days at 20°C or 5 days at 50°C. No decline in dimethachlor could be observed during the experiment and, therefore, no degradation half-lives can be calculated.

2.8.2.2.6 Photochemical degradation

Two GLP studies are available to assess the direct photodegadation of dimethachlor. The first study by Schmidt (1995) used the UV/VIS spectrum and GCSOLAR to calculate the maximum theoretical rate of direct photodegradation in surface water for 40°N and 50°N in summer. The half-lives amounted to 4520 days for 40°N and 8620 days for 50°N and indicate that direct phototransformation of dimethachlor in the environment is not a relevant degradation process. These half-lives exceed the limiting value of 30 days beneath which further studies were required. The spectral data clearly indicate that direct photolysis is not considered to be a relevant process for the fate of dimethachlor in the environment.

In the second study (Kirkpatrick, 1995b) investigated the aqueous photolysis of phenyl-U-^{14}C labelled dimethachlor in sterile aqueous buffer solutions at pH 7 at a concentration of 5 mg/L. Samples, in borosilicate glass tubes, were continuously irradiated with xenon arc light for up to 15 days. Although the borosilicate glass may have limited the radiation reaching the test solutions, dimethachlor was not photodegraded in sterile aqueous solution at pH 7. It can be concluded that photolysis is not likely to be a significant route of degradation of dimethachlor under these conditions.

Study 1 Schmidt (1995)

The susceptibility of the test item for direct phototransformation by sunlight in aquatic systems of the environment was determined.

The UV/VIS-spectra were measured with a double-beam spectrophotometer in dilute phosphate buffer of pH 7.4 with 10% acetonitrile added as co-solvent and decadic molar extinction coefficients were calculated according to the Beer-Lambert Law. Rate constants k_a and half-lives $t_{1/2}$ for direct photolysis in surface water for 40°N and 50°N in summer were calculated with the program GCSOLAR.

The absorption band of dimethachlor tails into the wavelength range of sunlight on the earth's surface with decadic molar extinction coefficients of

$\varepsilon = 1.4$ [1*mol^{-1}cm^{-1}] at 290 nm

$\varepsilon = 0.7$ [1*mol^{-1}cm^{-1}] at 295 nm

$\varepsilon < 0.4$ [1*mol^{-1}cm^{-1}], detection limit, at wavelengths $\lambda \geq 300$ nm.

The decadic molar absorption coefficients are far below the trigger value of $\varepsilon = 10$ at wavelengths >290 nm. According to Council Directive 94/37/EEC, Annex I, July 1994, § 2.9.2, direct phototransformation is not considered a relevant process and no further studies for the direct phototransformation in sunlight are required. The same conclusion results with the criteria in the OECD Guideline Draft Document of August 2000, according to which further studies are required only if decadic molar extinction coefficients were greater than 2 over at least 15 nm above the 295 cut-off of solar irradiation at the earth's surface.

Minimum phototransformation half-lives for dimethachlor in surface waters at latitudes 40°N and 50°N were estimated with GCSOLAR by assuming a hypothetical quantum yield equal to one. The half-lives amounted to 4520 days for 40°N and 8620 days for 50°N and indicate that direct phototransformation of dimethachlor in the environment is not a relevant degradation process. These half-lives exceed the limiting value of 30 days beneath which further studies were required.

The spectral data clearly indicate that direct photolysis is not considered to be a relevant process for the fate of dimethachlor in the environment. Therefore, direct phototransformation was not investigated further.

Study 2 Kirkpatrick (1995b)

The aqueous photolysis of dimethachlor, 2-chloro-N-(2,6-dimethylpheny1)-N-(2-methoxyethyl) acetamide was studied. Phenyl-U-^{14}C labelled dimethachlor (Batch No.: CFQ-7176-2; radiochemical purity: >99%; specific radioactivity: 2.57 MBq/mg) was added to sterile aqueous buffer solutions at pH 7 (0.01 M phosphate buffer containing 0.3% acetonitrile) at a concentration of 5 mg/L and was continuously irradiated with xenon arc light for up to 15 days using a Suntest Accelerated Exposure Unit (Heraeus). The emission spectrum of the xenon arc light was shown to be comparable to that of natural sunlight, radiation with a wavelength of less than 290 nm was filtered out. The average light intensity was between 2.6 and 3.2 W/m^2 in the wavelength range from 300 – 400 nm. The test vessels were made of borosilicate glass with an internal diameter of 2.5 cm and a height of 8.0 cm. Irradiated and dark control solutions were maintained at 25°C. Samples were analysed for radioactivity recovery and for relative proportions of dimethachlor and potential photodegradation products by means of HPLC and 2D TLC. Volatile radioactivity was collected with several trapping agents.

In irradiated and dark control solutions dimethachlor was not significantly degraded. Throughout the whole study period of 15 days, the test substance accounted for between 96.6% - 98.3% (irradiated solutions) and 97.0% - 98.8% (dark control solutions) of test solution radioactivity, respectively.

Recoveries of total radioactivity from test solutions were in the range 96.1 -100.2% of the applied radioactivity at all times. There was no detectable formation of volatile radioactivity or photoproducts of dimethachlor during irradiation equivalent to 39 days of natural sunlight at latitude 40°N.

Dimethachlor was not photodegraded in sterile aqueous solution at pH 7; therefore, it can be concluded that photolysis is not likely to be a significant route of degradation of dimethachlor under these conditions.

2.8.2.2.7 Other / Weight of evidence

Two soil adsorption/desorption studies are available. The first (Keller, 1984) is a non-guideline study, carried out prior to the implementation of GLP. The adsorption constants normalised for the organic carbon content (K_{OC}) ranged from 56.65 to 128 mL/g with an average K_{OC} value of 77.85 mL/g. This suggests that dimethachlor is a compound with a moderate adsorption capacity to most soils.

In the second study, performed to GLP, Burgener (1995) determined the adsorption/desorption characteristics of ^{14}C-phenyl ring labelled dimethachlor in 5 different soils using the batch equilibrium method. The adsorption constants normalised for the organic carbon content (K_{OC}) ranged from 29.72 to 95.37 mL/g with an average K_{OC} value of 62.51 mL/g. This suggests that dimethachlor would be classified as slightly mobile in soil.

Study 1 Keller (1984)

The adsorption and desorption properties of dimethachlor were studied in 5 different soils using the batch equilibrium method: Collombey, Switzerland (Soil I, loamy sand), Lakeland Florida, USA (Soil II, sand), Les Evouettes, Switzerland (Soil III, silt loam), Vetroz, Switzerland (Soil IV, silt loam) and Illarzaz, Switzerland (Soil V, silt loam).

Aqueous solutions of ^{14}C labelled dimethachlor with a specific radioactivity of 0.35 MBq/mg were prepared at five concentrations of 1.25, 2.5, 5.0, 10.0 and 20.0 mg a.s./L. The solutions (100 mL aliquots) were added to soil (10 to 50 g dry weight) and allowed to equilibrate while shaking for 24 hours at 20°C in sealed centrifuge tubes.

After equilibration the phases were separated by centrifugation. Dimethachlor concentrations in aqueous phases were determined directly by liquid scintillation counting (LSC), and indirectly by difference calculation between initial and measured levels in the aqueous phases for the soil phases. The wet soil pellets remaining after adsorption were desorbed twice with 100 mL fresh distilled water. The adsorption data were evaluated using the Freundlich equation and values for K_F (Freundlich sorption constant), K_{OC} (organic carbon sorption coefficient) and 1/n were determined, whilst for desorption only the amount of desorbed radioactivity was determined and presented as percent of the amount of adsorbed parent equivalent.

The Freundlich adsorption coefficient K_F varied between 0.46 mL/g for the Collombey loamy sand and 18.4 mL/g for the Illarzaz silt loam. The slopes (1/n) of the adsorption isotherms ranging from 0.90 to 0.95 with correlation coefficients >0.99 indicate that the experimental data were adequately described by the non linear Freundlich equation. The adsorption constants normalised for the organic carbon content (K_{OC}) ranged from 56.65 to 128 mL/g with an average K_{OC} value of 77.85 mL/g.

Dimethachlor is a compound with a moderate adsorption capacity to most soils. The results for desorption are presented as percent of the amount adsorbed. The sum of the percentage released in two desorption steps ranged from 41.8 to 73.1% indicating that adsorption was not a fully reversible process.

Table 81: Soil adsorption constants for dimethachlor in various soils

Parameter	**Soil I**	**Soil II**	**Soil III**	**Soil IV**	**Soil V**	Mean
	Collombey	**Lakeland**	**Les Evouettes**	**Vetroz**	Illarzaz	
Texture	loamy sand	sand	silty loam	silty loam	silty loam*	
pH	7.4	6.5	6.2	7.3	6.9	
% organic matter	1.4	1.0	2.6	9.3	43.1	
% organic carbon**	0.8	0.6	1.5	5.4	25.0	
% $CaCO_3$	10.2	0.1	0.1	55.6	7.8	
Adsorption						
K_F	0.46	0.76	1.18	3.72	18.4	
K_{OC}	56.65	128.0	62.0	69.0	73.6	77.85
1/n	0.90	0.90	0.92	0.92	0.95	0.92
Desorption						
Step 1	43.6	45.7	55.0	51.8	24.6	
Step 2	22.5	18.3	17.7	21.3	17.2	
∑ Step 1 + 2	66.1	64.0	72.7	73.1	41.8	

* Due to the high organic matter content, mechanical analyses could not be carried out; ** OC = OM/1.724

The Freundlich adsorption constants K_F determined for dimethachlor varied between 0.46 and 18.4 mL/g. Desorption occurred at a slower rate than adsorption which is shown by the amounts of dimethachlor measured at the two desorption steps.

Study 2 Burgener (1995)

The adsorption/desorption characteristics of ^{14}C-phenyl ring labelled dimethachlor was studied in 5 different soils using the batch equilibrium method: Collombey (Soil I, loamy sand), Speyer 2.1 (Soil II, sand), Les Evouettes (Soil III, silt loam), Vetroz (Soil IV, silt loam) and Illarzaz (Soil V, silt loam).

Solutions of analytical grade ^{14}C labelled dimethachlor (Batch no. CFQ 7176-2; specific radioactivity: 2.57 MBq/mg; radiochemical purity: >99%) were prepared in 0.01M calcium chloride at four concentrations of 0.1, 0.5, 1.0 and 2.5 mg a.s./L. Sterile $CaCl_2$ solutions (20 mL aliquots) were added to 2 mm sieved soil (8 g dry weight base) in Teflon centrifuge tubes, shaken and incubated at room temperature overnight. At the end of conditioning, 100 µL of the appropriate stock solution (^{14}C- dimethachlor dissolved in acetone and made up to the correct volume with 0.01M

$CaCl_2$) were added by means of a Hamilton syringe to the corresponding pre-conditioned suspension. The concentration of acetone in the aqueous phase was 0.1%. Duplicate test tubes were used per concentration except the highest concentration, which was run with four replicates.

After 22 hours of agitation (230 strokes per minute) at 20°C in the dark, the phases were separated by centrifugation (2600 rpm). Dimethachlor concentrations in aqueous phases were determined directly by liquid scintillation counting (LSC), and indirectly by difference calculation between initial and measured levels in the aqueous phases for the soil phases.

The wet soil pellets remaining after adsorption were desorbed twice with 20 mL of fresh 0.01M $CaCl_2$ solution under the same conditions as described before. Mass balances were performed for the two highest concentrations with samples set up additionally. The aqueous phases of these samples were analysed by HPLC. The soil pellets were extracted with acetone and acetone:water (8:2, v/v) and the extracts were analysed for parent content by TLC. Non-extractable radioactivity was determined by combustion analysis.

All data were evaluated using the Freundlich equation and values for K_F (Freundlich sorption constant), K_{OC} (organic carbon sorption coefficient) and 1/n were determined.

The mean total recoveries calculated from duplicate samples of all soils and concentrations ranged from 95.5% to 104.9%. Non-extractables amounted to 10.1%, 2.1%, 20.1%, 20.1% and 68.3% for soils I, II, III, IV and V, respectively. HPLC analysis of the aqueous phases after equilibration showed 98.8% to 100% of radioactivity as parent compound. The corresponding figures for the soil extracts were 98.5% to 99.1% as determined by TLC. After extraction with acetone and acetone:water 0.6 to 2.0% AR remained in the soil.

The Freundlich adsorption coefficient K_F varied between 0.32 mL/g for the Speyer sand and 13.3 mL/g for the Illarzaz silt loam. The slopes (1/n) of the adsorption isotherms ranging from 0.76 to 0.94 with correlation coefficients >0.99 indicate that the experimental data were adequately described by the Freundlich equation. The adsorption constants normalised for the organic carbon content (K_{OC}) ranged from 29.72 to 95.37 mL/g with an average K_{OC} value of 62.51 mL/g. Dimethachlor is a compound with a moderate adsorption capacity to most soils. The desorption K_{OC} values from the soils were somewhat higher than the adsorption values ranging from 42 to 133 and 33 to 196 mL/g for the 1st and 2nd desorption step, respectively. This might indicate that adsorption was not fully reversible.

Adsorption of ^{14}C- dimethachlor to soil was correlated with the organic carbon contents of the soils: Soils containing more organic carbon adsorbed higher amounts of test substance. When relating the adsorption constants to the organic carbon (or organic matter) content of the soils a mean K_{OC} of 62.51 mL/g (K_{OM} = 36.26 mL/g) was calculated which classify dimethachlor as slightly mobile in soil according the mobility classes introduced by Guth, 1985.

Table 82: Soil adsorption constants for 14C-dimethachlor in 5 soils

Parameter	**Soil I**	**Soil II**	**Soil III**	**Soil IV**	**Soil V**	Mean
	Collombey	**Speyer 2.1**	**Les Evouettes**	**Vetroz**	Illarzaz	
Texture	loamy sand	sand	silty loam	silty loam	silty loam	
pH	7.3	5.5	7.3	7.1	6.6	
% organic matter	2.02	1.14	3.62	7.57	33.34	
% organic carbon	1.17	0.66	2.70	4.39	19.34	
% $CaCO_3$	5.6	<0.1	3.5	55.7	4.7	
Adsorption						
K_F	1.12	0.32	1.47	1.30	13.30	
K_{OC}	95.37	48.72	69.97	29.72	68.77	62.51
1/n	0.9052	0.8515	0.8444	0.7598	0.9392	
1st Desorption						
K_F	1.55	0.48	2.19	1.83	16.43	
K_{OC}	133	72	105	42	85	
1/n	0.8772	0.8015	0.8449	0.8144	0.9576	
2nd Desorption						
K_F	2.29	0.68	2.89	1.45	18.01	
K_{OC}	196	103	138	33	93	
1/n	0.8899	0.7351	0.8265	0.7489	0.9604	

The test substance was moderately mobile in Soil I and slightly mobile in Soils II, Ill and V, and mobile in Soil IV. Based on K_{OC} and K_{OM} values averaged over the five soils, ^{14}C- dimethachlor was classified as slightly mobile ($K_{OC(mean)}$ = 62.51 mL/g).

2.8.3 Summary of fate and behaviour in air

Dimethachlor is classified as semi-volatile with some potential to be transported to air. A new vapour pressure study of dimethachlor parent has been conducted producing a revised endpoint of 2.3×10^{-3} Pa at 20 °C. The resulting new Henry's law constant is 2.8×10^{-4} Pa · m^3/mol at 20 °C. Based on these properties some volatilisation from soil and plant surfaces is expected to occur. The results of a laboratory controlled air flow experiment demonstrated that only 0.14% of the dimethachlor applied was lost to the air compartment in 24 hours. The low volatilisation was confirmed in non-guideline wind tunnel studies where the air concentrations at 6 and 24 hr after application were below the limit of detection. Furthermore deposition into water samples placed between 1 and 20 m from the applied area was very low over a 24 hr period.

The atmospheric half-life of dimethachlor is estimated at 3.2 hours under average atmospheric conditions. This indicates that the small proportion of applied dimethachlor that will volatilise would be unlikely to be subject to long range atmospheric transport.

Based on these findings, the environmental concentrations of dimethachlor in the atmosphere (PEC_A) would be expected to be extremely low or undetectable.

2.8.3.1 Hazardous to the ozone layer

Table 83: Summary table of studies on hazards to the ozone layer

Method	Results	Remarks	Reference
The rate constant for the reaction with OH-radicals was estimated according to the increment procedure described by R. Atkinson. This procedure allows an estimation of the degradation of a compound by OH-radicals in the atmosphere based on structure-reactivity relations. Computer program: Atmospheric oxidation program V 1.55a. Based on: Method of Atkinson (1988): Environ. Toxicol. Chem., 7, 435. Not GLP.	With an average concentration of OH-radicals of $1.5 * 10^6$ cm^{-3} oxidation of dimethachlor by hydroxyl radicals based on a 12 hours day revealed an estimated half-life (Atkinson method) ranging between 2.5 and 4.5 hours in the atmosphere.	The dominating degradation processes for dimethachlor are addition of hydroxyl radicals to the aromatic ring, reaction with N-fragments of the molecule and abstraction of hydrogen by hydroxyl radicals.	Stamm (1995)
The bimolecular rate coefficient for the reaction of dimethachlor in the atmosphere with hydroxyl radicals has been estimated using the method of Atkinson as developed in the Atmospheric Oxidation Program (AOPWIN) v1.92 .	The atmospheric half-life of dimethachlor estimated by AOPWIN v1.92 under average atmospheric conditions was estimated to be 3.174 hours.	Based on this short half-life, concentrations of dimethachlor in the in the atmosphere would be expected to be extremely low or undetectable	Pierce (2019)

2.8.3.1.1 Short summary and overall relevance of the provided information on hazards to the ozone layer

Calculations using the method of Atkinson for indirect photo oxidation in the atmosphere through reaction with hydroxyl radicals resulted in an atmospheric half life estimated at 2.5 to 4.5 hours (assuming an atmospheric hydroxyl radical concentration of 1.5×10^6 radicals/cm^3) indicating the small proportion of applied dimethachlor that will volatilise would be unlikely to be subject to long range atmospheric transport (Stamm, 1995).

A new calculation (Pierce, 2019) has been conducted using the current estimation software and is submitted for evaluation, the new atmospheric half-life is 3.2 hours.

2.8.3.1.2 Comparison with the CLP criteria

Dimethachlor is not listed in Annex I to Regulation (EC) No 1005/2009.

2.8.3.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

No classification is warranted.

2.8.4 Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

The leaching potential of dimethachlor and its metabolites has been assessed as outlined in the tiered assessment scheme of FOCUS 2014.

Dimethachlor is a pre and post emergent herbicide applied once in 3 year's rotation in winter and spring oilseed rape crops. Its major metabolites identified from aerobic laboratory degradation studies were CGA50266, CGA369873 and CGA354742 from either oxidative metabolism or glutathione reaction in soil. All dimethachlor metabolites are predicted to be very highly mobile from the McCall Classification[16] giving rise to significant predicted concentrations in groundwater.

As part of the tiered assessment, and to identify mobile fractions in the soil column, the leaching behaviour of dimethachlor applied at 1.5 kg/ha to a sand soil monolith was studied. No residues of dimethachlor were detected in the lysimeter leachate at 1 meter depth at any time point during the conduct of the study. The major metabolites identified from the percolate were CGA50266 and CGA354742 confirming that these are the two major soil metabolites of significance for the groundwater compartment, both showing potential to reach concentrations > 10 µg/L in lysimeter percolate. A number of additional metabolites were also identified in the leachate that were not observed as major metabolites in laboratory degradation studies:

- A number of downstream sulfonic acid metabolites – CGA373464, CGA369873[17] and SYN547047 (originally identified as SYN528702).
- A downstream oxidative degradation product – SYN530561

The four lysimeter metabolites CGA373464, CGA369873, SYN547047 (formerly identified as SYN528702) and SYN530561 were all identified at annual average concentrations significantly < 10 µg/L but > 0.1 µg/L as demonstrated in the table below. Concentrations of the metabolites tended to be highest in the year of the application.

Table 84: Summary of the annual average concentration of dimethachlor metabolites from an outdoor Borstel lysimeter monolith after application of 1.5 kg dimethachlor/ha

Metabolite	CGA50266	CGA354742	CGA369873	SYN 530561	SYN 547047**	CGA373464
Mean concentration* in leachate 1st year (µg/L)	28.1 / 36.2	35.1 / 32.4	2.5 / 1.7	2.0 / 2.1	6.7 / 11.3	1.5 / 3.3
Mean concentration* in leachate 2nd year (µg/L)	0.45 / 2.3	7.7 / 17.4	2.2 / 2.4	0.6 / 1.1	0.2 / 0.3	0.8 / 1.7
Mean concentration* in total leachate (µg/L)	13.3 / 17.6	20.5 / 24.1	2.3 / 2.1	1.2 / 1.6	3.2 / 5.2	1.2 / 2.4

[16] McCall et al., 1995

[17] CGA369873 is a common metabolite with metazachlor, a herbicide also predominantly used in oilseed rape, where the use overlaps with dimethachlor. As such, reported residues of CGA369873 have a combined contribution from both dimethachlor and metazachlor

* All concentrations given as µg parent equivalents / L. First value: lysimeter 24 / second value: lysimeter 25.
** originally identified as SYN 528702

Germany

In the original EU review, a groundwater monitoring study provided confidence that the metabolites would not exceed 10 µg/L under field conditions[18]. The experts agreed that, with the exception of the metabolite not analysed for (CGA 102935), in the regions monitored, a good indication was provided that a parametric level of 10 µg/L in groundwater was not exceeded for the metabolites sought. However the majority of the fate and behaviour experts indicated that they would wish to see comparable monitoring exercises carried out more extensively across Europe to see if this conclusion might be more generally applicable.

As such, the monitoring study in Germany was revisited in 2015, with 15 (up to 2017: 14) Federal groundwater wells selected in six regions of Germany (Schneider, 2019), to provide an updated analysis. The monitoring sites were chosen based on recommendations from the Federal State water authorities and based on the selection criteria outlined in the guidance paper from the German regulatory authorities for the explanation of plant protection product findings in groundwater (Aden et al, 2002[19]). The monitoring wells targeted areas with a high oils seed rape intensity (used as a surrogate for product use but subsequently confirmed through farmer surveys (Resseler, 2018) overlying shallow and vulnerable aquifers (groundwater levels are generally at about 1 – 10 m below ground level). The typical topsoil (0-30 cm) texture in the vicinity of the wells were sand and/or loam and the underlying sediments were dominated by sand and/or gravel. Till and other less permeable material may occur occasionally and result in semi-confined aquifer conditions. Overall, the environmental scenario around each well represents a vulnerable situation with regard to pesticide leaching due to the presence of permeable soils and subsoils in the vicinity of the wells and the shallow groundwater. Groundwater samples were collected on a monthly basis from October 2015 to December 2016, and then on a bimonthly basis from February 2017 to September 2019 in six regions in Germany: Schleswig-Holstein, Mecklenburg-Vorpommern, Altmark-Prignitz, Lower Saxony, Bavaria and Upper Rhine Valley (Ried).

The groundwater analyses are summarised in Table 85; it should be recognised that on the basis that for hydraulic connection could not be shown at present for Wernikow, Maria Einsiedel, Gross-Rohrheim, Brekendorf and Biblis this data has been excluded from further analysis on the basis of being a potential false negative.

Table 85: Summary of monitoring data for dimethachlor and its metabolites from 15* German Federal wells from October 2015 to September 2019

Analyte	Number of samples <LOQ	Number of samples >LOQ <trigger	Number of samples >trigger	90th percentile Tolerance Interval (µg/L)
DMT	306	0	0	0.025
CGA50266	295	11	0	0.15
CGA354742	160	139	7	4.42
CGA369873	37	259	10	4.89
CGA373464	306	0	0	0.025
SYN547047	306	0	0	0.025
SYN530561	306	0	0	0.025
CGA102935	306	0	0	0.025
CGA37734	306	0	0	0.025
CGA42443	306	0	0	0.025

* up to 2017 groundwater samples were taken from 14 groundwater monitoring wells

From a total of 306 samples, no residues of dimethachlor, CGA102935, CGA373464, SYN547047, CGA37734, CGA42443 and SYN530561 were observed in any sample at any timepoint which points to the leaching potential of these metabolites being very low.

In terms of residue analysis, only CGA354742, CGA369873 and CGA50266 were quantified >LOD in any sample, with the residues of the sulfonic acid metabolites (CGA354742 and CGA369873) being higher than CGA50266. Across the 306 samples, CGA50266 did not quantify > 0.75 µg/L in any sample and this is reflected by a 90th percentile for all samples in Germany of 0.15 µg/L, indicating a low risk of leaching. In the same samples, the 90th percentile

[18] EFSA Scientific Report (2008), 169, 1-111
[19] Aden K, Binner R, Fischer R, Gottschild, D, Kloskowski R, Schinkel K & Michalksi B (2002). Translation –"Protection of groundwater from entry of plant protection products: guidance on how to clarify findings and implement post registration monitoring activities". Federal Biological Research Centre of Agriculture and Forestry, Berlin.

groundwater concentrations of the sulfonic acids CGA354742 and CGA369873 were found to be 4.42 and 4.89 µg/L respectively, confirming the observation of the lower tiers that these metabolites have the highest potential to leach to groundwater but notably indicating a reduction in concentration versus those predicted by the FOCUS models. Across the study, only 7 samples from 306 (2.6 %) were found to be >10 µg/L for CGA354742 whilst for CGA369873 10 individual samples (2.7 %) were observed to exceed, with all of the samples having been collected at Kittlitz, a Federal monitoring well known to be extremely vulnerable.

The groundwater well at Kittlitz was evaluated and found to be in good condition and filtered in a sand and gravel aquifer with groundwater level varying between 2.6 and 4.6 m below ground level (bgl). The groundwater hydrochemistry shows a significant influence by agriculture as indicated by the nitrate concentrations of up to 280 mg/L. The site inspections, as well as the farmer interviews provided no evidence of improper use of plant protection products (PPP) or other abnormalities in the up-gradient area of the monitoring well. Residues of the sulfonic acid metabolites at the site rapidly declined to < 10 µg/L with the CGA354742 residue declining from 10.45 µg/L in February 2017 to < 0.75 in 2018 (see Figure 2.8.4-1).

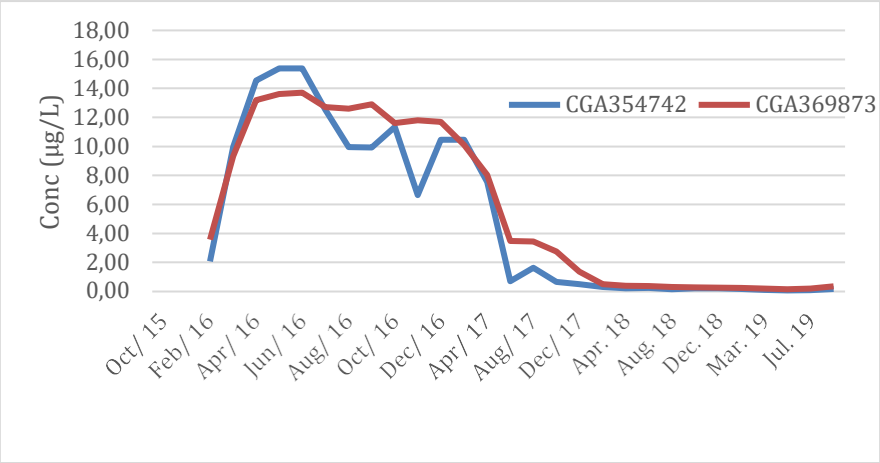


Figure 2.8.4-1: Overview of analytical results for Kittlitz, Germany

A similar trend was observed for CGA369873, indicating that although the sulfonic acid metabolites of dimethachlor have the potential to exceed the parametric limit of 10 µg/L, such exceedances are of a temporal nature with rapid reduction below the trigger.

Lithuania

As a condition of re-registration of dimethachlor containing products in Lithuania, monitoring was conducted at a number of field sites previously installed by Syngenta in highly vulnerable cereals fields. The field sites (referenced as LT-891, LT-822, and LT-823) have groundwater levels ranging between 1.96 and 3.77 m bgl, with USDA soil classifications of loamy sand (LT-822), sand (LT-823), and sandy clay loam (LT-891). Each field site was instrumented with a minimum of three sampling wells around the perimeter of the treated field, with one site instrumented with four wells (LT-891). Each field site received a minimum of one application of dimethachlor to the entire field, where site areas were between 3.49 – 35.47 Ha in size. Each field is characterised fully in terms of hydrogeology.

Initiating in December 2015, a total of 142 samples have been collected on a quarterly basis and analysed to date. For parent, in contrast to all of the previous analysis, a residue of dimethachlor was obtained > 0.1 µg/L at the first sampling event post well-installation, with this residue rapidly declining < 0.1 µg/L and then < the limit of quantification (LOQ). No further detectable residues of dimethachlor were observed in the study suggesting that the detection was a consequence of the well installation and annulus development rather than true leaching. As such, the Lithuanian study confirms the observations of the previous tiers that dimethachlor does not leach to groundwater.

The instrumentation of the field sites is such that the field is triangulated for the purposes of evaluating groundwater flow and increasing the likelihood that one of the wells is in the down gradient position. As such, not all wells can be connected to the treated field and the distribution analysis is only considered for wells in the down-gradient position to exclude false negatives.

The observation of residues of dimethachlor in a single timepoint from well LT-891 at the initiation of the study

correlated with the time of the original well installation procedure and is considered an artefact from the well installation and settling procedure. This is confirmed by all dimethachlor residues in all other samples <LOQ in this study.

No quantifiable residues of CGA373464, CGA42443 or CGA37734 were observed at any time point from any well, whilst residues of SYN530561 and CGA102935 were always < 0.75 µg/L. For CGA50266, the majority of the samples (92 %) quantified were < 1 µg/L, with the other analyses all < 10 µg/L indicating that although the metabolite has leaching potential, the monitoring results demonstrate reduced concentrations versus the lysimeter and point to a low potential for groundwater exceedance of the non-relevant threshold of 10 µg/L. This is reflected in the derived 90th percentile groundwater concentration of CGA50266 of 3.98 µg/L. Likewise, CGA369873 was only observed > 10 µg/L from a single sample from LT-891 with a 90th percentile (tolerance interval) concentration of 5.22 µg/L, representing a low overall risk of exceedances.

In contrast, the sulfonic acid metabolite CGA354742 was found to be > 10 µg/L in multiple samples collected from LT-823. A detailed site investigation at LT-823 highlighted a potential for reverse flow of the groundwater table which will have contributed to the elevated residues. Nevertheless, the monitoring confirms the observation of the early tiers that CGA354742 has a high leaching potential with the 90th percentile (tolerance interval) determined as 9.90 µg/L.

Overall, the findings in Lithuania confirm the observations from Germany where leaching of the sulfonic acid metabolites > trigger values was found to occur at a low underlying frequency with such exceedance only occurring at very vulnerable sites and being short lived in nature. The derived 90th percentile GW concentrations were < 10 µg/L for all dimethachlor metabolites.

France

In 2007 a monitoring study was initiated to investigate the residues of dimethachlor (CGA17020) and its metabolites CGA50266, CGA354742, CGA369873, CGA373464, SYN528702, SYN530561, CGA102935 and CGA37734 in groundwater throughout the major oil seed rape growing regions of France. The study focused on monitoring diverse aquifer types dominant in France, with a final definitive list of 31 wells currently being monitored.

During the period 2007 to 2017, a total of 1230 groundwater samples were taken over 47 sampling intervals from the sampling sites validated for oil seed rape cropping and use of dimethachlor-containing products. These were analysed for dimethachlor, CGA50266, CGA354742, CGA369873, CGA373464, SYN547047 (from 2012), SYN530561, CGA102935, CGA37734 and CGA42443 (from 2014).

Of the 1230 samples, dimethachlor has only been detected (0.05-0.08 µg/L) in six groundwater samples (0.5 % of all samples) from well DMT-94-18 (September 2013, June and September 2014, April and June 2015 and September 2016) with no exceedances observed. No quantifiable residues (> 0.05 µg/L) of the metabolites CGA373464, SYN547047, CGA37734 and CGA42443 were determined in any of the samples. Likewise, no sample was found to contain a residue of CGA50266, CGA102935 or SYN530561 > 0.1 µg/L, with detection of these metabolites >LOQ being sporadic.

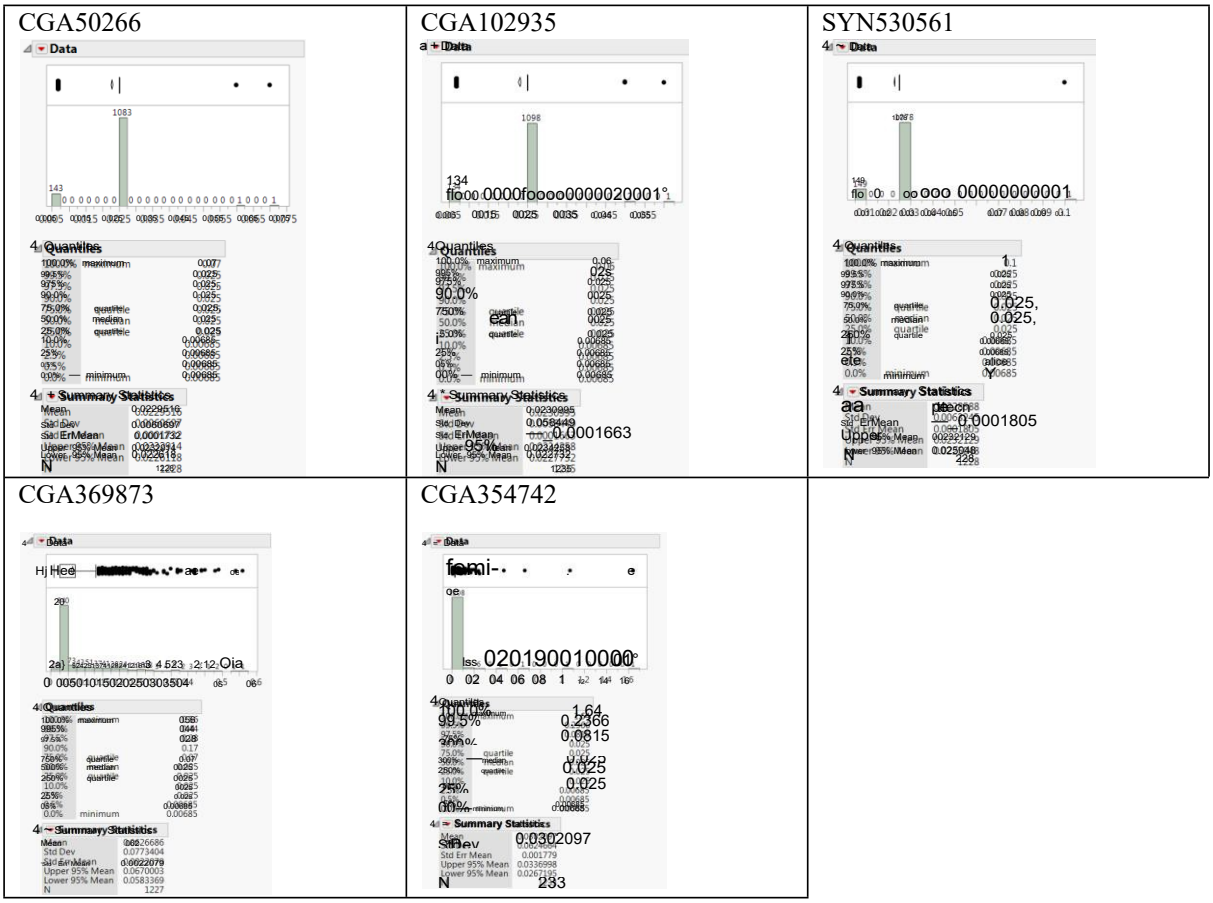


Figure 2.8.4-2: Residues of dimethachlor and its metabolites from a Syngenta Tier 4 monitoring in France

As indicated from the Germany and Lithuanian monitoring, CGA354742 and CGA369873 were the most frequently detected analytes in the study. However, in contrast to those studies, from a total of 1233 samples, only 25 quantifiable residues of CGA354742 were found (2 %) with a maximum residue of 1.64 µg/L returning a 90th percentile (tolerance interval) of 0.025 µg/L. This indicates an overall low risk of leaching in the monitored wells and confirms that exceedances are restricted to extremely shallow and vulnerable groundwater settings only. For CGA369873, an increased detection rate >LOQ (348 samples from 1227 representing 28 %) potentially highlights the increased contribution of metazachlor in these regions, however the maximum residue was 0.56 and the 90th percentile (tolerance interval) 0.17 µg/L.

Investigation of ADES findings

During a discussion with ANSES, the very low level of metabolites was questioned by the Regulatory Authority and Syngenta were challenged to confirm that the metabolite residues observed are representative of France (since National monitoring does not address metabolite levels). As such, a step-wise approach was used to identify potential ADES wells that could be incorporated into the Syngenta study, with 11 wells finally being identified as potentially suitable monitoring locations. It should be noted that one of the key steps was to use detection of dimethachlor in ADES wells as an indicator of product use in the catchment.

Groundwater samples were taken at 18 intervals between June-September 2014 and December 2017. Overall, 153 of the total number of 169 samples analysed for dimethachlor showed no quantifiable residue. Of the eleven wells selected, 7 wells showed no exceedances of dimethachlor across the period of monitoring. Of the other 4 wells, a number of exceedances were observed with some significant concentrations observed > 0.1 µg/L. The wells sampled had been selected from ADES on the basis of showing historical detections of dimethachlor and as such observation of detectable residues of parent was anticipated. As a consequence that this was an unusual observation in the context of the tiered assessment, two elucidations were conducted to understand the local situation (Schofield, Borwin, and Andrews, 2019). In summary, the elucidation identified significant karstic features in the local landscape which represented fast flow pathways, directing residues of dimethachlor rapidly from the surface to groundwater via sinkholes and fractures and reflects the extremely complex and localised geological conditions at the sites.

In terms of the dimethachlor metabolites, generally low levels of the metabolites were observed with no exceedances

of the 10 µg/L at any time point for any analyte. For metabolites CGA373464, SYN547047, SYN530561 and CGA37734, no residues greater than the LOQ of 0.05 µg/L were observed at any time, except for SYN547047 where residues were detected in well DMTn-17-70 (1.89 µg/L and 0.17 µg/L in September 2016 and September 2017 respectively) and for SYN530561 where residues were detected in wells DMTn-37-51 (0.09 µg/L in February 2015) and DMTn-17-70 (0.16 µg/L in September 2016). Varying residues of the metabolites CGA50266, CGA354742, CGA369873 and CGA102935 were observed (see Figure 2.8.4-3) but with no exceedances of the 10 µg/L. Considering the conclusion of the elucidations, it was considered that the generally low level observed for the dimethachlor metabolites supported the theory that the parent compound had spent very little time residing in the soil to allow for degradation processes to occur.

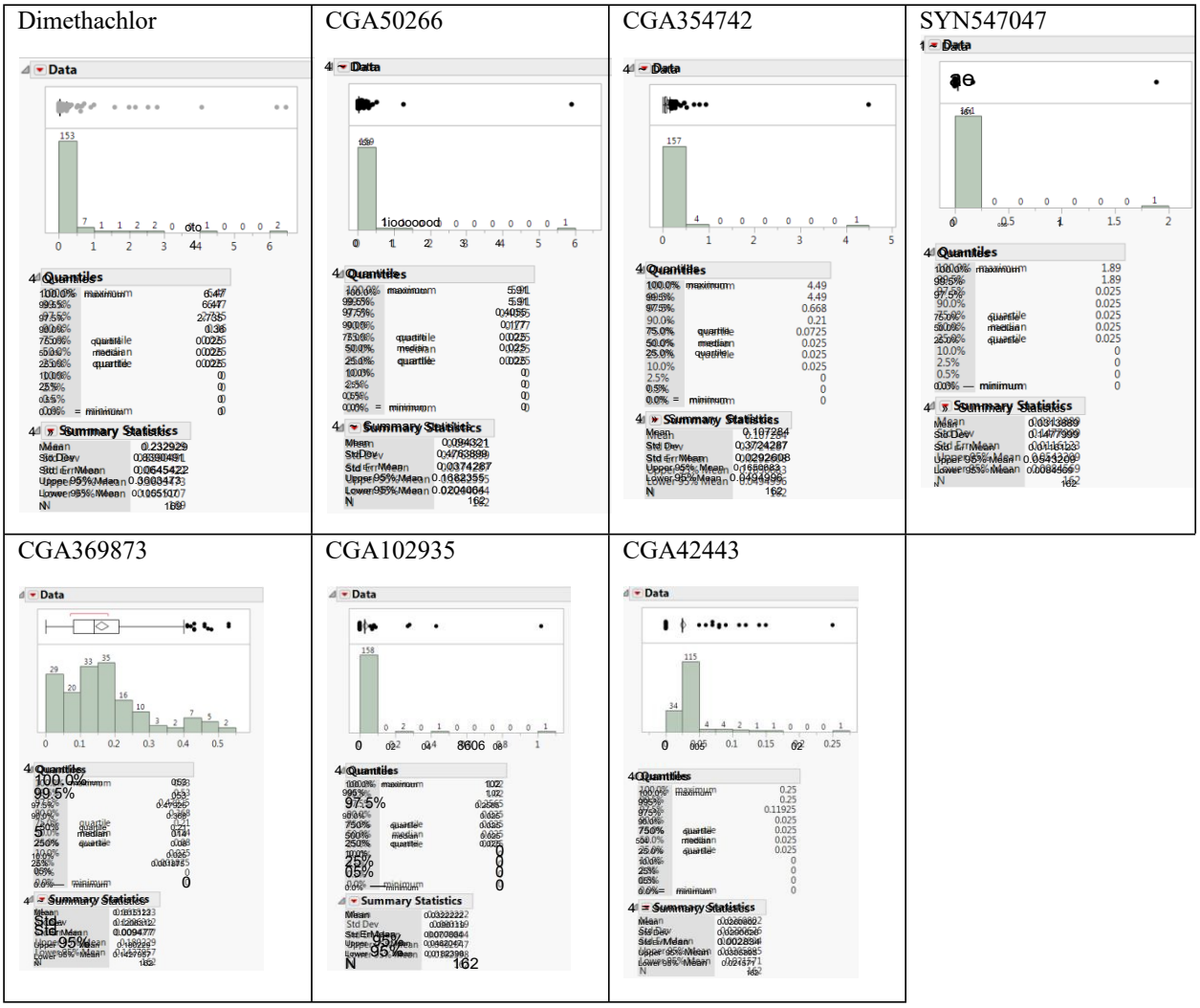


Figure 2.8.4-3: Residues of dimethachlor and its metabolites from ADES well monitoring in France

Overall conclusion

An assessment of the leaching potential of dimethachlor and its metabolites CGA50266, CGA354742, CGA369873, CGA373464, SYN547047, SYN530561, CGA102935, CGA37734 and CGA42443 has been conducted in line with the tiered assessment. Dimethachlor is not predicted to leach to the groundwater compartment as predicted through the tiered assessment. The Tier 1 modelling indicates a very low risk, and this is confirmed through tiers 3 and 4. An observation of an exceedance at a recently installed well in Lithuania was taken to be a direct consequence of the well installation process. Further, the observation of elevated concentrations in limited regions in France were concluded to be a consequence of significant karstic features in the landscape which allowed for the direct entry of dimethachlor to fast flow pathway leading to exceedances of the trigger. It should be noted that these conditions are extremely localised, with the elucidation identifying potential geological conduits at the field scale. Overall, the leaching potential of dimethachlor under chromatographic leaching conditions is very low, as demonstrated by the FOCUS

PEARL and PELMO tier 1 predictions, the lysimeter studies and the monitoring in oilseed rape growing regions of Germany, France and Lithuania.

Considering metabolites, both the model and/or the lysimeter indicated a high leaching potential of CGA50266, CGA354742, SYN547047 and CGA369873 but assessment at tier 4 demonstrates that the predicted concentrations appear to be conservative versus measured residues. In particular, measured concentrations of CGA50266 and SYN547047 appear to be significantly over estimated at the lower tiers (see Table 86) with no exceedances of either metabolite across the monitoring studies. The tiered assessment however did confirm the observation at the lower tiers that CGA354742 and CGA369873 (the sulfonic acid metabolites) have the greatest leaching potential and these metabolites have the potential to exceed the non-relevant limit under very vulnerable conditions. However, it should be noted that the exceedances of the parametric limit occurred at very few locations geographically, specifically those defined as extremely shallow groundwater overlain by vulnerable sandy soils, with the monitoring demonstrating that these exceedances are very short lived with rapid reduction below 10 µg/L. The highest concentration for CGA354742 was found at a site in Lithuania with a site investigation demonstrating that the site's groundwater flow has the potential to reverse; as such the concentrations reported at this site are not representative. Overall, 90th percentiles for the individual monitoring studies demonstrated safe use as outlined in Table 86 considering FOCUS (2014) and Gimsing et al[20] (2019).

A summary of the tiered assessment of the leaching potential of dimethachlor metabolites considered relevant within the groundwater risk assessment is given in the table below.

Table 86: Summary of the tiered assessment of dimethachlor metabolites

TIER	Study	CGA 42443	CGA 50266	CGA 102935	CGA 354742	SYN 547047	CGA 369873	CGA 373464	SYN 530561
1	FOCUS modelling	**Overall 80th Percentile PEC$_{GW}$ at 1 m Soil Depth [µg/L]**							
		0.679	19.0	0.929	20.8	0.518	24.5	0.193	1.23
3	Lysimeter	**Annual average concentrations in leachate [µg/L]**							
		-	36.2	-	35.1	11.3	2.5	3.3	2.1
4	Groundwater monitoring	**90th percentile residues in groundwater [µg/L]**							
Germany		0.025	0.15	0.025	4.42	0.025	4.89	0.025	0.025
Lithuania		**0.025**	**3.98**	**0.17**	**9.90**	**0.40**	**5.22**	**0.025**	**0.025**
France		0.025	0.025	0.025	0.025	<LOQ	0.17	0.025	0.025
ADES		0.025	0.18	0.025	0.21	0.025	0.37	0.025	0.025

2.8.5 Definition of the residues in the environment requiring further assessment

In accordance with the requirements of Commission Regulation (EU) No 283/2013 the components considered for the residue definition for risk assessment are as follows:

Soil

Dimethachlor is extensively degraded in soil to a number of metabolites which are observed at greater than 5% of applied radioactivity. Therefore parent and the following metabolites are considered in the definition of the residue in soil: Dimethachlor (CGA017020), CGA42443, CGA50266, CGA102935, CGA354742 and SYN547047.

Groundwater

[20] Gimsing, A.L., Agert, J., Baran, N. et al. J Consum Prot Food Saf (2019). https://doi.org/10.1007/s00003-019-01211-x

Dimethachlor is extensively degraded in soil to a number of metabolites observed at greater than 5% of applied radioactivity which are potentially mobile and could reach ground water. Therefore parent and the following metabolites are considered in the definition of the residue in groundwater: Dimethachlor (CGA017020), CGA42443, CGA50266, CGA102935, CGA354742, CGA369873, CGA373464, SYN530561 and SYN547047.

Surface water and sediment

Dimethachlor is degraded in water to two metabolites (CGA50266, CGA42443) which are observed at greater than 5% of applied radioactivity. Therefore parent and metabolites CGA42443 and CGA50266 are considered in the definition of the residue in surface water and dimethachlor only is considered in the definition of the residue for sediment.

Air

Dimethachlor is of moderate volatility and its polar metabolites are not expected to be volatile. Therefore dimethachlor only should be considered in the definition of the residue for risk assessment in air.

2.8.6 Summary of exposure calculations and product assessment

Soil

The initial as well as the maximum short-term and long-term predicted concentrations of parent dimethachlor in soil (PEC_S) after application in a single year were calculated using the ESCAPE model (v2.0, 5 September 2017) (results shown in Document *Dimethachlor_RAR_20_Volume_3CP_A5089H_B-8*, Table 8.2-2). Since dimethachlor dissipates rapidly in soil, calculation of the potential accumulation of dimethachlor in soil following repeated triennial applications of A5089H was not triggered and not performed.

The PEC_S of metabolites CGA42443, CGA50266, CGA102935, CGA354742 and SYN547047 have been assessed with the FOCUS groundwater crop interception values and the worst case laboratory DT_{50} values as shown in Document *Dimethachlor_RAR_10_Volume_3CA_B-8*. PEC_S immediately after the first application were calculated using the PEC Soil Calculator Version 1.0 (Microsoft Excel) as well as the maximum, the short-term and the long-term PEC_S values after application in a single year.

Simplified Degradation Pathway for Dimethachlor in Soil

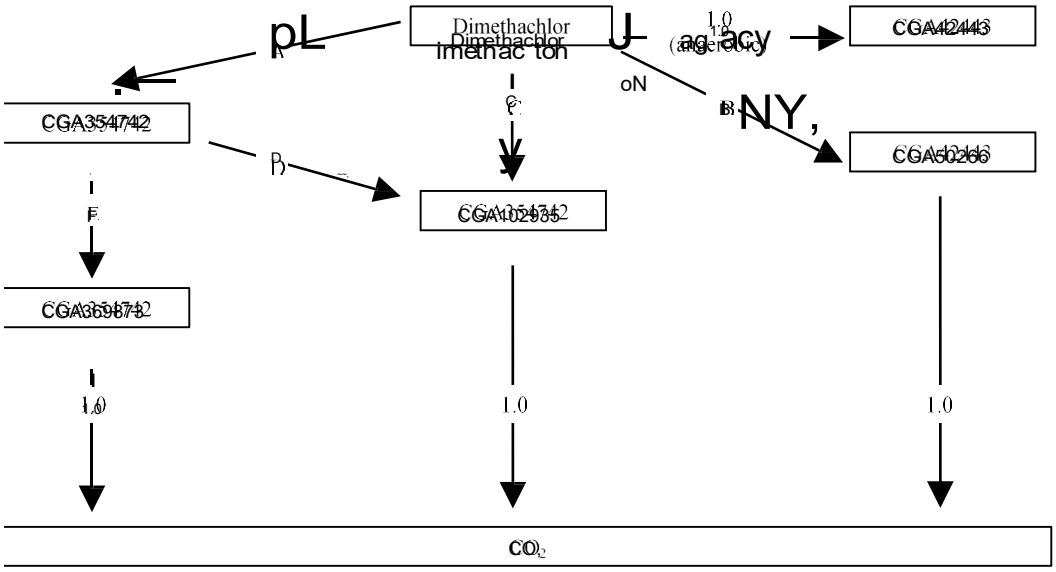


Figure 2.8.6-1: Simplified Degradation Pathway for Dimethachlor in Soil

The potential accumulation of the dimethachlor metabolites CGA42443, CGA50266, CGA354742 and SYN547047 was calculated and is reported in Document *Dimethachlor_RAR_20_Volume_3CP_A5089H_B-8*, tables 8.2-5 to -9 and table 8.2-C1. The dimethachlor metabolite CGA102935 dissipates rapidly in soil and calculation of its potential accumulation in soil following repeated triennial applications of A5089H was not triggered and not performed.

The initial soil concentrations of the formulated product A5089H, applied to winter and spring oilseed rape was predicted with and without crop interception (results shown in Document *Dimethachlor_RAR_20_Volume_3CP_A5089H_B-8,* Table 8.2-10).

Groundwater

The estimation of PEC_{GW} for dimethachlor and its relevant metabolites has been carried out according to current guidance, using standard FOCUS scenarios and outputs from MACRO in FOCUS 5.5.4, FOCUS PELMO 5.5.3 and FOCUS PEARL 4.4.4 models.

Dimethachlor and five significant soil metabolites (CGA42443, CGA50266, CGA102935, CGA354742 and SYN547047) were considered for groundwater risk assessment based on the endpoints derived from laboratory soil degradation and mobility studies. Furthermore, the metabolites CGA369873, CGA373464 and SYN530561, observed in lysimeter leachate but not detected at significant levels in the laboratory soil degradation studies, were also considered for groundwater risk assessment.

The predicted concentration of parent dimethachlor in groundwater **(**PEC_{GW}) was < 0.1 µg/L for all modelled uses. In fact, predicted PEC_{GW} were < 0.001 for all uses, except for one scenario – Piacenza, use on winter oil seed rape without crop interception; max PEC_{GW} of 0.006 and 0.011 µg/L for 750 g a.s./ha and 1000 g a.s./ha, respectively.

The worst case PEC_{GW} for all metabolites exceeded 0.1 µg/L for all uses in one or more scenarios except for CGA42443 on winter oilseed rape (750 g a.s./ha, BBCH 20) and SYN547047 on winter oilseed rape (750 and 1000 g a.s./ha, BBCH 20) and spring oilseed rape (750 g a.s./ha, BBCH 00) (overall maximum PEC_{GW} shown in table 87, below).

Table 87: Overall maximum PEC_{GW} of dimethachlor and soil metabolites CGA42443, CGA50266, CGA102935, CGA354742 and SYN547047 for application of dimethachlor to winter and spring oilseed rape (MACRO in FOCUS 5.5.4, FOCUS-PEARL 4.4.4, FOCUS-PELMO 5.5.3)

Crop	**80th Percentile PEC_{GW} at 1 m Soil Depth [µg/L] [a]**					
	Dimethachlor	**CGA42443**	**CGA50266**	**CGA102935**	**CGA354742**	**SYN547047**
Winter oilseed rape 1 x 750 g a.s./ha (BBCH 00)	0.006	0.488	14.2	0.686	15.5	0.296
Winter oilseed rape 1 x 750 g a.s./ha (BBCH 20)	<0.001	0.082	3.19	0.179	3.20	0.010
Winter oilseed rape 1 x 1000 g a.s./ha (BBCH 00)	0.011	0.679	19.0	0.929	20.8	0.518
Winter oilseed rape 1 x 1000 g a.s./ha (BBCH 20)	<0.001	0.116	4.26	0.242	4.31	0.023
Spring oilseed rape 1 x 750 g a.s./ha (BBCH 00)	<0.001	0.243	14.1	0.355	14.6	0.084
Spring oilseed rape 1 x 1000 g a.s./ha (BBCH 00)	<0.001	0.339	18.7	0.485	19.7	0.171

[a] maximum PEC_{GW} across all scenarios and from either MACRO in FOCUS, FOCUS-PEARL or FOCUS-PELMO simulations

Table 88: Overall maximum PEC_{GW} of dimethachlor and lysimeter metabolites CGA369873, CGA373464 and SYN530561 for application of dimethachlor winter and spring oilseed rape (FOCUS-PEARL 4.4.4, FOCUS-PELMO 5.5.3, MACRO in FOCUS 5.5.4)

Crop	80th Percentile PEC_{GW} at 1 m Soil Depth [µg/L] [a]		
	CGA369873	CGA373464	SYN530561
Winter oilseed rape 1 x 750 g a.s./ha (BBCH 00)	18.2	0.144	0.901
Winter oilseed rape 1 x 750 g a.s./ha (BBCH 20)	3.33	0.030	0.288
Winter oilseed rape 1 x 1000 g a.s./ha (BBCH 00)	24.5	0.193	1.23
Winter oilseed rape 1 x 1000 g a.s./ha (BBCH 20)	4.49	0.041	0.390
Spring oilseed rape 1 x 750 g a.s./ha (BBCH 00)	12.6	0.134	0.075
Spring oilseed rape 1 x 1000 g a.s./ha (BBCH 00)	16.7	0.180	0.103

[a] maximum PEC_{GW} across all scenarios and from either MACRO in FOCUS, FOCUS-PEARL or FOCUS-PELMO simulations

The relevance of metabolites exceeding 0.1 µg/L in groundwater modelling is evaluated and presented in Vol 1, Section 2.12 of this document.

Surface water and sediment

The predicted environmental concentrations (PEC_{SW} and PEC_{SED}) of dimethachlor and metabolites formed in surface water and sediment have been generated according to current guidance with the FOCUS surface water models at STEP 1-2 and for dimethachlor additionally at STEP 3 and STEP 4. The FOCUS tool SWASH (v 5.3), including the operational models FOCUS-MACRO (v 5.5.4), FOCUS-PRZM (v 4.3.1) and FOCUS-TOXSWA (v 5.5.3), were used in the modelling for Step 3 simulations. The ECPA tool SWAN (v 5.0.0) was used to implement mitigation options at Step 4. Dimethachlor and two metabolites (GA42443 and CGA50266) are included in the definition of the residue for the surface water risk assessment.

Additionally, exposure estimates were also generated for soil metabolites CGA102935, CGA354742 and SYN547047 (based on the endpoints derived from laboratory soil degradation and mobility studies) and metabolites CGA369873, CGA373464 and SYN530561 (observed in lysimeter leachate but were not detected in the laboratory soil or aquatic degradation studies). The models were run with the representative use patterns of single applications to winter and spring oilseed rape.

Complete calculations are presented in Document *Dimethachlor_RAR_20_Volume_3CP_A5089H_B-8, B.8.5.*

2.9 EFFECTS ON NON-TARGET SPECIES

2.9.1 Summary of effects on birds and other terrestrial vertebrates

Effects on birds

Table 89: Summary of toxicity endpoints for birds

Organism	Test type	Endpoints	Proposed endpoint for risk assessment	Reference (author, date, Syngenta Ref)
Japanese quail (*Coturnix coturnix japonica*)	Acute oral	LD_{50} = 524 mg/kg bw	LD_{50} = 524 mg/kg bw	[redacted] ***(1994) CGA17020/0272***

Japanese quail (*Coturnix coturnix japonica*)	Sub-chronic and reproductive	NOAEL = 98.91 mg/kg bw/d (900 mg/kg diet)	LD_{50}/10 of 52.4 mg/kg bw/d	[redacted] ***(1995)*** ***CGA17020/0295***

Effects on mammals

Table 90: Summary of toxicity endpoints for mammals

Organism	Test item	Test type	Endpoint	Reference (author, date, Syngenta Ref)
Rat	Dimethachlor	Acute oral	LD_{50} = 1600 mg/kg bw	[redacted] ***(1973)*** ***CGA17020/0106***
Rat	A5089F	Acute oral	LD_{50} >2000 mg/kg bw	[redacted] ***(1995)*** ***CGA17020/0329***
Rat	CGA50266	Acute oral	LD_{50} >2000 mg/kg bw	[redacted] ***(1994)*** ***CGA50266/0001***
Rat	CGA354742	Acute oral	LD_{50} >2000 mg/kg bw	[redacted] ***(1995)*** ***CGA354742/0003***
Rat	SYN550004	Acute oral	LD_{50} >2000 mg/kg bw	[redacted] ***&*** [redacted] ***(2019)*** ***SYN550004_10000***
Rat	Dimethachlor	Chronic oral	NOAEL = 20 mg/kg bw/day	[redacted] ***(1994)*** ***CGA17020/0270***

2.9.2 Summary of effects on aquatic organisms [section 11.5 of the CLH report]

2.9.2.1 Bioaccumulation [equivalent to section 11.4 of the CLH report template]

2.9.2.1.1 Estimated bioaccumulation

The experimentally derived Log Kow (also referred to as Log Pow) of dimethachlor is 2.17. As such dimethachlor is not expected to bioaccumulate in aquatic organisms. For classification and labelling purposes a substance with Log Kow <4 may be considered unlikely to bioaccumulate in aquatic organisms.

2.9.2.1.2 Measured partition coefficient and bioaccumulation test data

For pesticide registration, a Log Kow >3 triggers the requirement for a bioconcentration study. Since the Log Kow of dimethachlor is <3 no BCF study was submitted or required.

Overall, dimethachlor is not expected to bioaccumulate in aquatic organisms. This is further confirmed in two publicly available papers which looked at potential bioaccumulation of dimethachlor in fish. Both papers were considered reliable and relevant and both confirm that dimethachlor does not bioaccumulate in fish.

The first paper (Lazartigues et al. 2013; CGA017020_10345) was undertaken to determine the biomagnification factors (BMFs) and half-lives of dimethachlor in common carp (*Cyprinus carpio*) and Eurasian perch (*Perca fluvialitis*) over a 6-day uptake phase and 12-day depuration phase. Fish were exposed to a mixture of 13 pesticides including dimethachlor in treated feed. Calculated BMFs were based on analyses of dimethachlor in feed and fish muscle tissues using LC-MS/MS.

The steady state BMF for dimethachlor in carp muscle tissue was calculated to be 3.6E-05, with a half-life of 7.2 days. Steady state was not attained for perch within the exposure period, therefore the kinetic BMF for dimethachlor in perch muscle tissue was 3.3E-05, with a half-life of 18.7 days.

The second paper (Lazartigues et al. 2013; CGA017020_10344) analysed dimethachlor residues in water, sediment and muscle tissues of carp (*Cyprinus carpio*), roach (*Rutilus rutilus*) and Eurasian perch (*Perca fluviatilis*), from five managed ponds in north-eastern France, during two sampling periods. Dimethachlor residues were detected in water samples below the limit of quantification (LOQ; <0.01 µg dimethachlor/L) and up to 0.05 µg dimethachlor/L at the

most cultivated sites. Dimethachlor residues in sediment samples were reported to be <LOQ (<0.2 µg dimethachlor/kg wet weight). Dimethachlor was below the limit of detection (LOD; value not reported) in all fish muscle tissue samples.

2.9.2.2 Acute aquatic hazard [equivalent to section 11.5 of the CLH report template]

Table 91: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results (mg/L)	Key or Supportive study	Remarks	Reference
Acute toxicity to fish, OECD 203 Flow-through 96 hours	Rainbow trout *(Oncorhynchus mykiss)*	Dimethachlor (CGA17020) 96.8%	LC_{50} 5.9 (mm)	Key study	GLP	[redacted] (1993a) CGA17020/0211
Acute toxicity to fish, OECD 203 Flow-through 96 hours	Common carp (*Cyprinus carpio*)	Dimethachlor (CGA17020) 96.8%	LC_{50} 7.6 (mm)	Key study	GLP	[redacted] (1993b) CGA17020/0212
Acute toxicity to fish, No OECD Guideline available[2] Flow-through 96 hours	Rainbow trout *(Oncorhynchus mykiss)*	Dimethachlor (CGA17020) Purity not reported	LC_{50} 3.9 (nom)	Study does not meet the validity criteria.	Non-GLP[1]	[redacted] and CGA50266/0007
	Crucian carp (*Carassius carassius*)		LC_{50} 8.0 (nom)			
	Black bullhead catfish (*Ictalurus melas*)		LC_{50} 10.0 (nom)			
	Bluegill sunfish (*Lepomis macrochirus*)		LC_{50} 15.0 (nom)			
	Guppy (*Lebistest reticulatus*)		LC_{50} 7.4 (nom)			
Acute toxicity to fish, OECD 203 Flow-through 96 hours	Rainbow trout *(Oncorhynchus mykiss)*	A5089F 497 g/L dimethachlor (CGA17020)	LC_{50} 9.5 (mm)	Key study	GLP	[redacted] (1996) CGA17020/0377
Daphnia sp Acute Immobilisation OECD 202 Static 48 hours	*Daphnia magna*	Dimethachlor (CGA17020) 96.8 %	LC_{50} 24 (nom)	Key study	GLP	Grade (1994a) CGA17020/0273
Daphnia sp Acute Immobilisation OECD 202 Static 48 hours	*Daphnia magna*	A5089F 497 g/L dimethachlor (CGA17020)	LC_{50} 18.1 (nom)	Key study	GLP	Neumann (1996) CGA17020/0382
Freshwater Algal Growth Inhibition, OECD 201 Static	*Desmodesmus subspicatus*	Dimethachlor (CGA17020) 96.8 %	E_rC_{50} 0.072 (nom)	Key study	GLP	Grade (1993c) CGA17020/0210 Stats re-analysis Schuster (2018)

72 hours			NOE_rC n.d.			CGA017020_10287
Freshwater Algal Growth Inhibition, OECD 201 Static 72 & 96 hours	*Anabaena flos-aquae*	Dimethachlor (CGA17020) 96.8 %	96 hour E_rC_{50} > 48.2 NOE_rC 12.3 72 hour E_rC_{50} > 48.2 NOE_rC 48.2 (mm)	Study does not meet the validity criteria. A new study is provided.	GLP	Palmer and Krueger (1998) CGA17020/0485
Freshwater Algal Growth Inhibition, OECD 201 Static 72 & 96 hours	*Anabaena flos-aquae*	Dimethachlor (CGA17020) 99.5 %	96 hour E_rC_{50} > 100 NOE_rC 100 72 hour E_rC_{50} > 100 NOE_rC 31.3 (mm)	Key study	GLP	Falk (2016) CGA017020_10167
Freshwater Algal Growth Inhibition, OECD 201 Static 72 hours	*Pseudokirchneriella subcapitata (*previously *Selenastrum capricornutum)*	A5089F 497 g/L dimethachlor (CGA17020)	E_rC_{50} 0.024 NOE_rC 0.013 (nom)	Study does not meet the validity criteria. A new study is provided	GLP	Van der Kolk (1996) CGA17020/0373
Freshwater Algal Growth Inhibition, OECD 201 Static 72 & 96 hours	*Pseudokirchneriella subcapitata (*previously *Selenastrum capricornutum)*	A5089H 494 g/L dimethachlor (CGA17020)	96 hour E_rC_{50} 0.029 NOE_rC 0.010 72 hour E_rC_{50} 0.034 NOE_rC 0.0032 (nom)	Key study	GLP	Volz (2006) CGA17020/0778
Lemna sp Growth Inhibition Test, OECD 221 Semi-static 7 days	*Lemna gibba*	Dimethachlor (CGA17020) 97.2%	E_rC_{50} 0.0658 NOE_rC 0.005 (nom)	Key study	GLP	Memmert (1999) CGA17020/0528
Lemna sp Growth Inhibition	*Lemna gibba*	A5089H	Frond no.	Key study	GLP	Liedtke (2011) A5089H_10003

Test, OECD 221 Static 7 days		495 g/L dimethachlor (CGA17020)	E_rC_{50} 0.063 NOE_rC n.d. <u>Dry weight</u> E_rC_{50} > 0.12 NOE_rC n.d.			
Lemna sp Growth Inhibition Test, OECD 221 Static 7 days	*Lemna gibba*	A5089F 497 g/L dimethachlor (CGA17020)	<u>Frond no.</u> E_rC_{50} 0.048 NOE_rC n.d. <u>Dry Weight</u> NOEC 0.008 (nom)	Key study	GLP	Grade (2002) CGA17020/0591

[1]Procedure for evaluation of acute toxicity of Pesticides to fish and Wildlife (1964). Bathe et al (1972)
[2] When the study was performed GLP had not been formally adopted for this study type; the study was performed according to sound scientific principles
Results are based on mean measured (mm) or nominal (nom) concentrations as indicated

2.9.2.2.1 Acute (short-term) toxicity to fish

Table 92: Table of endpoints to assess risk from dimethachlor and A5089H

Organism	Test item	Endpoints (mg/L)	Reference (author, date, Syngenta Ref)
Rainbow trout (*Oncorhynchus mykiss*)	A5089F	96 h LC_{50} = $9.5_{(mm)}$ (static) (4.72 mg a.s./L)	[redacted] ***(1996)*** ***CGA17020/0377***
	Dimethachlor	96 h LC_{50} = $5.9_{(mm)}$ (static)	[redacted] ***(1993a)*** ***CGA17020/0211***
Common carp (*Cyprinus carpio*)	Dimethachlor	96 h LC_{50} = $7.6_{(mm)}$ (static)	[redacted] ***(1993)*** ***CGA17020/0212***
Rainbow trout (*Oncorhynchus mykiss*)	CGA354742	96 h LC_{50} = $>100_{(nom)}$ (static test)	[redacted] ***(1995)*** ***CGA354742/0005***
Rainbow trout (*Oncorhynchus mykiss*)	CGA50266	96 h LC_{50} = $>100_{(nom)}$ (static test)	[redacted] ***(1995)*** ***CGA50266/0010***

Three reported studies describe the short-term acute toxicity of dimethachlor to fish across a range of species. The lowest reliable EC_{50} is considered to be 5.9 mg/L, based on nominal concentrations ([redacted], 1993). This value is considered appropriate to use for classification of acute toxicity to fish.

One study on the formulation A5089F ([redacted] 1996) is also provided as supporting information.

Study 1 [redacted] (1993a)

The toxicity of dimethachlor to rainbow trout (*Oncorhynchus mykiss*) was determined in a 96 hour acute toxicity test performed under static conditions. Fish were exposed to nominal dimethachlor concentrations of 1.0, 1.8, 3.2, 5.8 and 10 mg/L alongside a dilution medium control. Measured concentrations ranged from 69 to 98% and 71 to 88% of nominal at the start and end of the test, respectively.

Based on measured concentrations at the end of the exposure period, the 96 hour LC_{50} for dimethachlor to *Oncorhynchus mykiss* was 5.9 mg/L with 95% confidence limits of 4.8 to 7.3 mg/L. The 96 hour no observed effect concentration (NOEC) was determined to be 4.1 mg/L.

Study 2 [redacted] (1993b)

The toxicity of dimethachlor to the common carp (*Cyprinus carpio*) was determined in a 96 hour acute toxicity test performed under static conditions. Fish were exposed to nominal dimethachlor concentrations of 5.8, 10, 18, 32 and 58 mg/L alongside a dilution medium control. Measured concentrations ranged from 88 to 116% and 77 to 98% of nominal at the start and end of the test, respectively.

Based on measured concentrations at the end of the exposure period, the 96 hour LC_{50} for dimethachlor to *Cyprinus carpio* was 7.6 mg/L with 95% confidence limits of 5.8 to 9.2 mg/L. The 96 hour no observed effect concentration (NOEC) was determined to be 5.2 mg/L.

Study 3 [redacted] (1996)

The acute toxicity of A5089F to rainbow trout (*Oncorhynchus mykiss*) was determined under static conditions. Fish were exposed to nominal concentrations of 1.4, 2.6, 4.6, 8.3 and 15 mg/L, alongside a dilution water control. Measured concentrations of dimethachlor determined at the beginning and end of the exposure period were 105 to 120% and 105 to 112% of the nominal concentrations, respectively.

Based on mean measured concentrations, the 96 hour LC_{50} was 9.5 mg/L. The 96 hour NOEC, based on mortality, was 5.4 mg/L.

2.9.2.2.2 Acute (short-term) toxicity to aquatic invertebrates

Table 93: Table of endpoints to assess risk from dimethachlor and A5089H

Organism	Test item	Endpoints (mg/L)	Reference (author, date, Syngenta Ref)
Daphnia magna	A5089F	48 h EC_{50} = $18.1_{(nom)}$ (static) (9 mg a.s./L)	***Neumann (1996) CGA17020/0382***
	Dimethachlor	48 h EC_{50} = $24_{(nom)}$ (static)	***Grade, R. (1994a) CGA17020/0273***
	CGA354742	48 h EC_{50} >$100_{(nom)}$ (static)	***Neumann, Ch. (1995) CGA354742/0009***
	CGA50266	48 h EC_{50} >$100_{(nom)}$ (static)	***Neumann, Ch. (1995) CGA50266/0016***

mm - mean measured concentration
nom - nominal concentration

There is one reported study on the acute toxicity of dimethachlor to aquatic invertebrates (*Daphnia magna* (Grade, 1994a). The reported EC_{50} of 24 mg/L, based on nominal concentrations (with supporting analysis), is considered appropriate to use for classification purposes.

One study on the formulation A5089F (Neumann, 1994) is also provided as supporting information.

Study 1 Grade (1994a)

The toxicity of dimethachlor to the freshwater invertebrate *Daphnia magna* was determined under static conditions. *Daphnia magna* were exposed to nominal concentrations 10, 18, 32, 58 and 100 mg/L alongside a dilution medium control. Measured concentrations at 0 and 48 hours ranged from 94 to 99% of nominal.

Based on nominal concentrations, the 48 hour EC_{50} for dimethachlor to *Daphnia magna* was 24 mg/L, with 95% confidence limits of 21 to 27 mg/L. The 48 hour NOEC was determined to be 18 mg/L.

Study 2 Neumann (1996)

The toxicity of A5089F to the freshwater invertebrate *Daphnia magna* was determined under static conditions. *Daphnia magna* were exposed to nominal concentrations 10.4, 12.5, 18.0, 21.6, 26.0 and 31.0 mg/L alongside a dilution medium control. Measured concentrations at 0 and 48 hours ranged from 98.1 to 102.4% of nominal.

Based on nominal concentrations, the 48 hour EC_{50} for A5089F to *Daphnia magna* was 18.1 mg/L. The 48 hour NOEC was determined to be 12.5 mg/L.

2.9.2.2.3 Acute (short-term) toxicity to algae or aquatic plants

Several reported studies describe the toxicity of dimethachlor and dimethachlor formulations to algae and aquatic plants. These species groups are clearly far more sensitive than fish and aquatic invertebrates, as would be expected for an herbicide. Table below **shows the acute growth endpoints for these studies.**

The lowest reliable EC_{50} for acute classification purposes is considered to be 0.0658 mg/L for *Lemna gibba*, based on inhibition of growth rate (Memmert, 1999). Lower EC_{50} values reported for formulations A5089H and A5089F are not strictly suitable for classification purposes, which should be based on tests conducted with the active ingredient only. Nevertheless, the EC_{50} values for formulated products are within the same order of magnitude of the EC_{50} values for dimethachlor and therefore provide useful supporting information.

Table 94: Summary of acute growth endpoint for algae and aquatic plants

Test type	Test substance	Test species	Endpoint	Value (mg/L)	Reference
Acute toxicity to algae and aquatic plants	Dimethachlor technical	*Desmodesmus subspicatus*	72 h E_rC_{50}	0.0721	Grade (1993c); CGA17020/0210 Stats re-analysis Schuster (2018) *CGA017020_10287*
		Anabaena flos-aquae	96 h E_rC_{50} 72 h E_rC_{50}	>48.2 >48.2	Palmer and Krueger (1998) CGA17020/0485 Study does not meet the validity criteria. A new study is provided
		Anabaena flos-aquae	96 h E_rC_{50} 72 h E_rC_{50}	>100 >100	Falk (2016) CGA017020_10167
	A5089F 497 g/L dimethachlor	*Pseudokirchneriella subcapitata*	72 h E_rC_{50}	0.024	Van der Kolk (1996) CGA17020/0373 Study does not meet the validity criteria. A new study is provided
	A5089H 494 g/L dimethachlor	*Pseudokirchneriella subcapitata*	72 h E_rC_{50} 96 h E_rC_{50}	0.034 (0.017 mg a.s./L) 0.029	Volz (2006) CGA17020/0778 Stats re-analysis: Schuster (2018) A5089H_10409

Study 1 Grade (1993c) *CGA17020/0210* (Stats re-analysis Schuster (2018) *CGA017020_10287)*

The toxicity of dimethachlor to the freshwater green alga *Desmodesmus subspicatus* (formerly known as *Scenedesmus subspicatus*) was determined under static conditions. Algae were exposed to nominal concentrations 0.0041, 0.0123, 0.0369, 0.1107 and 0.33 mg/L alongside a culture medium control. Measured concentrations ranged from 79 to 93% and 76 to 85% of nominal, at the start and end of the exposure period, respectively.

The 72 hour E_rC_{50} has been subsequently been recalculated from the original data (Schuster 2018). The calculated 72 hour E_rC_{50} was 0.0721 mg/L with 95 % confidence limits of 0.0678 to 0.0765 mg/L.

Study 2 Falk (2016) *CGA017020_10167*

The toxicity of dimethachlor to the freshwater alga *Anabaena flos-aquae* was determined in a 96 hour static test. Algae were exposed to nominal concentrations 0.954 3.05, 9.77, 31.3 and 100 mg/L alongside a culture medium control. Measured concentrations at the start and end of the test were in the range of 91% to 98% and 92% to 101% of nominal, respectively.

Based on nominal concentrations, the 72 hour E_rC_{50} was >100 mg/L. The 96 hour E_rC_{50} was >100 mg/L.
The 72 hour NOEC for growth rate was 31.3 mg/L. The 96 hour NOEC for growth rate 100 mg/L.

Study 4 Volz (2006) *CGA17020/0778* (Stats re-analysis: Schuster (2018) *A5089H_10409)*

The toxicity of A5089H to the freshwater green alga *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capricornutum*) was determined. Algae were exposed to nominal concentrations of 0.00032, 0.001, 0.0032, 0.010, 0.032 and 0.10 mg/L alongside a culture medium control. Measured concentrations ranged from 84 to 91% and 62 to 86% of nominal at the start and end of the test, respectively.

Based on nominal concentrations, the 72 hour E_rC_{50} value for *Pseudokirchneriella subcapitata* exposed to A5089H was 0.034 mg/L. The 72 hour NOECs for growth rate was determined to be 0.0032 mg A5089H/L.

The 96 hour E_rC_{50} values was 0.029 mg/L. The 96 hour NOE_rC was 0.010 mg/L.

2.9.2.2.4 Acute (short-term) toxicity to other aquatic organisms

No additional studies.

2.9.2.3 Long-term aquatic hazard [equivalent to section 11.6 of the CLH report template]

Table 95: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results	Relevant study	Remarks	Reference
Fish Prolonged Toxicity Test, OECD 204 Flow-through 21 days	Rainbow trout *(Oncorhynchus mykiss)*	Dimethachlor (CGA17020) 96.8%	NOEC > 0.85 mg/L (mm)	Supporting study	GLP	[redacted] (1993d) CGA17020/0209
Fish Early Life Stage Toxicity, OECD 210 Flow-through 30 days	Zebra fish (*Danio rerio*)	Dimethachlor (CGA17020) 98.5%	NOEC = 1.0 mg/L (nom)	Key study	GLP	[redacted] & [redacted] (2018) CGA017020_10280
Daphnia magna Reproductio, OECD 211 Static-renewal	*Daphnia magna*	Dimethachlor (CGA17020) 96.8%	NOEC = 2.3 mg/L (mm)	Key study	GLP	Grade, R. (1994b) CGA17020/0288 Stats re-analysis:

22 days						Kümmich (2019) CGA017020_10346
Sediment-Water Chrironomid Toxicity , OECD 218 Static 28 days	*Chironomus riparius*	Dimethachlor (CGA17020) 97.2%	NOEC = 25.0 mg/kg (mm)	Key study	GLP	Wallace et al (2001) CGA17020/0589 Stats re-analysis: Kümmich (2019) CGA017020_10347
Daphnia magna Reproductio, OECD 211 Static-renewal 21 days	*Daphnia magna*	A5089F 502 g/L dimethachlor (CGA17020)	NOEC 1.0 mg/L (nom) (0.5 mg a.s./L)	Key study	GLP	Peither (2000) CGA17020/0579
Lemna sp Growth Inhibition Test, OECD 221 Static 7 days	*Lemna gibba*	Dimethachlor (CGA17020) 97.2%	NOE_rC 0.005 (nom)	Key study	GLP	Memmert (1999) CGA17020/0528 Stats re-analysis: Kümmich (2018) CGA017020_10283
Lemna sp. Growth Inhibition test, FIFRA Subdivision J, Series 123-2 Semi-static 14 days	*Lemna gibba*	Dimethachlor (CGA17020) 96.8%	NOEC 0.000464 (mm)		GLP Study not relevant for risk assessment or classification [1]	Palmer and Krueger (1999) CGA17020/0488 Stats re-analysis: Kümmich (2018) CGA017020_10282

Results are based on mean measured (mm) or nominal (nom) concentrations as indicated

[1] This study was considered to be acceptable during the previous EU review of dimethachlor (DAR, 2007). However, the endpoint for this study was not considered to be suitable for risk assessment because of (1) the low initial pH of 4.8-5.2, whereas an initial pH of 7.5 is recommended in OECD Guideline 221, (2) Despite the high water solubility of dimethachlor (2300 mg as/L at 20°C) an organic solvent was used which and it was expected that the use of this solvent has altered the toxicity. A recent publication (Bundschuh et al. 2016; Syngenta file number NA_14984) has shown that 95% of European surface waters receiving pesticide inputs have a pH between 7.0 and 8.5. The lower 2.5th percentile pH value was 6.7. This further confirms that this study should not be used for the current risk assessment and for classification and labelling purposes.

2.9.2.3.1 Chronic toxicity to fish

Two studies on dimethachlor, with supporting specific analysis, provides chronic toxicity data for fish ([redacted]1993; [redacted] & [redacted], 2018). The reported NOEC of >0.85 mg/L from the prolonged toxicity study ([redacted], 1993d) is not strictly suitable for classification purposes, due to limitations of the test guideline used and the fact that no effects

were observed at any treatment concentration. However, based on the available data, fish are not expected to be a sensitive species for dimethachlor. Therefore, the NOEC of 1.0 mg/L from the fish early life stage study ([redacted] & [redacted], 2018) should be used.

Study 1 [redacted] (1993d) *CGA17020/0209*

The chronic toxicity of dimethachlor to *Oncorhynchus mykiss* was determined under flow-through conditions according to OECD 204 Test Guideline. Fish were exposed for 21 days to nominal dimethachlor concentrations of 0.004, 0.016, 0.064, 0.25 and 1.0 mg/L alongside a dilution water control. Corresponding mean measured concentrations were 0.0036, 0.014, 0.058, 0.21 and 0.85 mg/L (84-91 % of nominal).

Mortality or symptoms of toxicity were not observed in any of the treatment groups. Similarly, exposure to dimethachlor did not have a significant effect on fish weight or length. Therefore, based on mean measured concentrations, the 21 day NOEC for dimethachlor in rainbow trout was >0.85 mg/L.

The OECD 204 Test Guideline does not consider early life stages, so is limited in its ability to predict chronic toxicity to fish. Hence it is provided here primarily as supporting information.

Study 2 [redacted] & [redacted] (2018) *CGA017020_10280*

The chronic toxicity of dimethachlor to *Danio rerio* was determined under flow-through conditions according to OECD 210 Test Guideline. Fertilised eggs were exposed to concentrations of 0.03, 0.1, 0.3, 1.0 and 3.0 mg test item/L under-flow-through conditions, alongside a control.

The NOEC for hatching success was 3 mg test item/L, the highest concentration tested. The NOEC for 30 days post hatch (DPH) survival was 1.0 mg test item/L. The EC_{10} and EC_{20} for post-hatch survival were 0.92 and 1.24 mg test item/L, respectively. For body length, the $EC_{10/20}$ values could not be determined. The NOEC for body length was determined to be 3.0 mg test item/L, while the LOEC could not be determined. For body fresh weight and dry weight, the $EC_{10/20}$ values could not be determined. The NOEC for body weight was determined to be 3.0 mg test item/L, while the LOEC could not be determined. Based on nominal concentrations, the overall NOEC was determined to be 1.0 mg/L and the LOEC was 3.0 mg/L.

2.9.2.3.2 Chronic toxicity to aquatic invertebrates

Table 96: Table of endpoints to assess risk from dimethachlor and A5089H

Organism	Test item	Endpoints (mg/L)	Reference (author, date, Syngenta Ref)
Daphnia magna	A5089F	21 d NOEC = 1.0 $_{(nom)}$ (0.5 mg a.s./L)	***Peither (2000) CGA17020/0579***
	Dimethachlor	EC_{10} = 2.18$_{(mm)}$ (static renewal) (number of offspring per live female)	***Grade, R. (1994b) CGA17020/0288 Stats re-analysis: Kümmich (2019) CGA017020_10346***
Chironomus riparius	Dimethachlor	EC_{10} = 15.6$_{(mm)}$ (static)	***Wallace et al., (2001) CGA17020/0589 Stats re-analysis: Kümmich (2019) CGA017020_10347***

mm - mean measured concentration
nom - nominal concentration

Two studies on dimethachlor showed long-term toxicity to aquatic invertebrates. The lowest NOEC of 2.3 mg/L (Grade, 1994b) is considered appropriate to use for classification purposes.

Study 1 Grade (1994b) *CGA17020/0288* Stats re-analysis: Kümmich (2019) *CGA017020_10346*

The chronic toxicity of dimethachlor to the freshwater invertebrate *Daphnia magna* was investigated under semi-static conditions. *Daphnia magna* neonates were exposed to nominal concentrations 0.01, 0.04, 0.16, 0.64, 2.5 and 10 mg/L

alongside a dilution medium control with renewal of the test solutions occurring three times a week. Ten replicates, each containing a single *Daphnia* were exposed to each test concentration and the control. Analysis of the test solutions indicated that dimethachlor concentrations were within 88 to 95% of nominal.

Based on mean measured concentrations, the 22 day NOEC for dimethachlor to *Daphnia magna* was 2.3 mg/L.

Study 2 Wallace et al (2001) *CGA17020/0589* Stats re-analysis: Kümmich (2019) *CGA017020_10347*

The chronic toxicity of dimethachlor to larvae of *Chironomus riparius* (<48 hours old) was investigated in a 28 day test under static conditions. Eighty animals (20 x four replicates) were exposed to test concentrations of 1.1, 3.3, 10, 30, 91 and 280 mg/kg dry weight of sediment. Mean measured concentrations in the sediment phase were 0.20, 0.57, 1.7, 4.7, 25 and 100 mg/kg. Mean measured concentrations in the overlying water phase were <0.014, 0.042, 0.13, 0.46, 4.0 and 23 mg/L, and in pore water were <0.11, <0.096, <0.097, 0.22, 0.71, 5.9 and 29 mg/L.

Based on mean measured sediment concentrations, the 28 day NOEC, based on the number of emerged adult insects, was 25 mg/kg dry weight. The corresponding concentrations in the overlying water and pore water were 4.0 mg/L and 5.9 mg/L, respectively.

Study 3 Peither (2000) *CGA17020/0579*

The chronic toxicity of A5089F to the freshwater invertebrate *Daphnia magna* was investigated under semi-static conditions. Ten replicates, each containing a single *Daphnia* were exposed to nominal concentrations 0.037, 0.11, 0.33, 1.0, 3.0 and 9.0 mg/L alongside a dilution medium control each test concentration and the control. Analysis of the test solutions indicated that dimethachlor concentrations were within 95.2 to 121% of nominal.

Based on nominal concentrations of A5089F the overall NOEC for the reproduction of *Daphnia magna* was concluded to be 1.0 mg/L.

2.9.2.3.3 Chronic toxicity to algae or aquatic plants

Several reported studies describe the chronic toxicity of dimethachlor and dimethachlor formulations to algae and aquatic plants. These species groups are clearly far more sensitive that fish and aquatic invertebrates, as would be expected for an herbicide. The algae and aquatic plant studies are used to derive both acute and chronic endpoints. One additional study (Palmer and Krueger, 1999) provides a 14 day endpoint which is described below, however this study has deficiencies which make it unsuitable for classification purposes (see below). Table below **shows the chronic growth endpoints for these studies.**

The most reliable endpoint for chronic classification purposes is considered to be the NOEC of 0.005 mg/L for *Lemna gibba*, based on inhibition of growth rate (Memmert, 1999). Lower NOEC value reported for formulation A5089H (Volz, 2006) is not strictly suitable for classification purposes, which should be based on tests conducted with the active ingredient only. Nevertheless, the NOEC values for formulated products are within the same order of magnitude as the NOEC value for dimethachlor and therefore provide useful supporting information.

Table 97: Summary of chronic growth endpoints for algae and aquatic plants

Test type	Test substance	Test species	Endpoint	Value (mg/L)	Reference
Chronic toxicity to algae and aquatic plants	Dimethachlor technical	*Lemna gibba*	7 d NOEC	**0.005**	Memmert (1999) CGA17020/0528 Stats re-analysis: Kümmich (2018) CGA017020_10283
		Lemna gibba	14 d NOEC	0.000464	Palmer and Krueger (1999)[1] CGA17020/0488 Stats re-analysis: Kümmich (2018) CGA017020_10282

Test type	Test substance	Test species	Endpoint	Value (mg/L)	Reference
	A5089H 495 g/L dimethachlor	*Lemna gibba*	Frond no.: 7 d NOE_rC Dry Weight: 7 d NOE_rC	nd nd	Liedtke (2011) A5089H_10003 Stats re-analysis: Kümmich (2018) A5089H_10402
	A5089F 497 g/L dimethachlor	*Lemna gibba*	Frond no.: 7 d NOE_rC	0.008	Grade (2002) CGA17020/0591 Stats re-analysis: Kümmich (2018) A5089F_10022

nd = not determined

[1] This study was considered to be acceptable during the previous EU review of dimethachlor (DAR, 2007). However, the endpoint for this study was not considered to be suitable for risk assessment because of (1) the low initial pH of 4.8-5.2, whereas an initial pH of 7.5 is recommended in OECD Guideline 221, (2) Despite the high water solubility of dimethachlor (2300 mg as/L at 20°C) an organic solvent was used which and it was expected that the use of this solvent has altered the toxicity. A recent publication (Bundschuh et al. 2016; Syngenta file number NA_14984) has shown that 95% of European surface waters receiving pesticide inputs have a pH between 7.0 and 8.5. The lower 2.5th percentile pH value was 6.7. This further confirms that this study should not be used for the current risk assessment and for classification purposes.

Study 1 Memmert (1999) *CGA17020/0528* (Stats re-analysis: Kümmich (2018) *CGA017020_10283)*

The toxicity of dimethachlor to the freshwater aquatic plant *Lemna gibba* was determined in a 7 day semi-static test system. Fronds of *L. gibba* were exposed to nominal dimethachlor concentrations of 0.0016, 0.005, 0.015, 0.050 and 0.160 mg/L alongside a dilution medium control. The exposure solutions were renewed every 48 or 72 hours and the concentrations of dimethachlor in the solutions was verified by HPLC analysis of samples collected from the fresh and aged solutions at the start of the study and each renewal period. Measured concentrations dimethachlor ranged from 75 to 123 % of the nominal values.

Based on nominal concentrations the 7 day EC_{50} values for the effects of dimethachlor on growth rate was 0.0658 mg/L. The 7 day NOE_rC for the effects of dimethachlor on growth rate was 0.005 mg/L.

Study 2 Liedtke (2011) *A5089H_10003* (Stats re-analysis: Kümmich (2018) *A5089H_10402)*

The toxicity of A5089H to the freshwater aquatic plant *Lemna gibba* was determined in a 7 day static test system, followed by testing for recovery of growth. Lemna plants were exposed for seven days to nominal A5089H concentrations of 0.005, 0.01, 0.02, 0.04, 0.08 and 0.120 mg/L, plus a dilution water control. The measured concentrations of A5089H (based on the active ingredient dimethachlor) ranged from 105 to 109% and 87 to 94% of nominal at the start and end of the 7 day exposure period.

For classification purposes, the recovery phase of this study is not relevant, however the results at 7 day provide relevant supporting information.

Based on nominal concentrations, for frond number the 7 day E_rC_{50} was 0.063 mg/L. The 7 day E_rC_{50} based on dry weight could not be determined, but was >0.12 mg/L.

After 28 days in test medium free of test item, complete recovery of *Lemna gibba* was observed for all concentrations assessed.

Study 3 Grade (2002) *CGA17020/0591* (Stats re-analysis: Kümmich (2018) *A5089F_10022)*

The toxicity of A5089F to the freshwater aquatic plant *Lemna gibba* was determined in a 7 day static test system. Fronds were exposed to nominal A5089F concentrations of 0.0010, 0.0020, 0.0040, 0.0080, 0.016, 0.032 and 0.064 mg/L alongside a culture medium control. Measured concentrations ranged from 92 to 107% and 79 to 107% of nominal at the start and end of the test, respectively.

Based on nominal concentrations and reduction in frond number the 7 day E_rC_{50} and E_bC_{50} were determined to be 0.048 mg/L and 0.033 mg/L, respectively. The NOEC for reduction in the number of fronds and dry weight was 0.008 mg/L.

2.9.2.3.4 Chronic toxicity to other aquatic organisms

No additional studies.

2.9.2.4 Comparison with the CLP criteria

2.9.2.4.1 Acute aquatic hazard

Table 98: Summary of information on acute aquatic toxicity relevant for classification

Method	Species	Test material	Results	Remarks	Reference
Acute toxicity to fish, OECD 203 Static system 96 hours	Rainbow trout *(Oncorhynchus mykiss)*	Dimethachlor (CGA17020) 96.8 %	LC_{50} 5.9 mg/L (mm)	GLP	[redacted] (1993) CGA17020/0211
Daphnia sp Acute Immobilisation OECD 202 Static 48 hours	*Daphnia magna*	Dimethachlor (CGA17020) 96.8 %	EC_{50} = 24 mg/L (nom)	GLP	Grade (1994a) CGA17020/0273
Acute toxicity to algae OECD 201 72 hours	*Desmodesmus subspicatus*	Dimethachlor (CGA17020) 96.8 %	E_rC_{50} = 0.0721 mg/L	GLP	Grade (1993c) CGA17020/0210
Lemna sp Growth Inhibition Test, OECD 221 Semi-static 7 days	*Lemna gibba*	Dimethachlor (CGA17020) 97.2 %	E_rC_{50} = 0.0658 mg/L	GLP	Memmert (1999) CGA17020/0528 Stats re-analysis: Kümmich (2018) CGA017020_10283

Based on these results the most sensitive species group are aquatic plants with an E_rC_{50} = 0.0658 mg/L. On this basis, the following classification and labelling of dimethachlor is proposed:

Aquatic Acute 1 H400 (Very toxic to aquatic life); as the lowest $L(E)C_{50}$ is > 0.01 and < 0.1 mg/L the associated M-factor is 10.

2.9.2.4.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Table 99: Summary of information on long-term aquatic toxicity relevant for classification

Method	Species	Test material	Results	Remarks	Reference
Fish Early Life Stage Toxicity, OECD 210 Flow-through 30 days	Zebra fish *(Danio rerio)*	Dimethachlor (CGA17020) 98.5 %	NOEC = 1.0 mg/L (nom)	GLP	[redacted] & [redacted] (2018) CGA017020_10280
Daphnia magna Reproduction, OECD 211 Static-renewal 22 days	*Daphnia magna*	Dimethachlor (CGA17020) 96.8 %	NOEC = 2.3 mg/L (mm)	GLP	Grade (1994b) CGA17020/0288 Stats re-analysis: Kümmich (2019) CGA017020_10346
Acute toxicity	*Desmodesmus subspicatus*	Dimethachlor (CGA17020)	NOE_bC = 0.037 mg/L	GLP	Grade (1993c)

to algae OECD 201 72 hours		96.8 %			CGA17020/0210 Stats re-analysis: Schuster (2018)
Lemna sp Growth Inhibition Test, OECD 221 Static 7 days	*Lemna gibba*	Dimethachlor (CGA17020) 97.2 %	NOEC = 0.005 mg/L (nom)	GLP	Memmert (1999) CGA17020/0528 Stats re-analysis: Kümmich (2018) CGA017020_10283

Based on these results the most sensitive species group are aquatic plants with a NOEC = 0.005 mg/L.

Bioaccumulation

For pesticide registration, a Log Kow >3 triggers the requirement for a bioconcentration study. Since the Log Kow of dimethachlor is <3 no BCF study was submitted or required. The experimentally derived Log Kow of dimethachlor is 2.17. For classification and labelling purposes a substance with Log Kow <4 may be considered unlikely to bioaccumulate in aquatic organisms. As such dimethachlor is not expected to bioaccumulate in aquatic organisms.

Degradation

Available studies show that dimethachlor is not readily biodegradable and not rapidly degraded by hydrolysis or photolysis in the aquatic environment. In open water systems, there was no evidence of significant degradation of dimethachlor. In water/sediment systems, the formation of strongly bound residues was a major pathway for dissipation of dimethachlor and its metabolites.

Overall, based on the data available, dimethachlor is considered not to be rapidly degradable for classification purposes.

On this basis, the following classification and labelling of dimethachlor is proposed:

Aquatic Chronic 1 H410 (Very toxic to aquatic life with long lasting effects); as the lowest chronic NOEC is between 0.001 and 0.01 mg/L the associated M-factor is 10.

2.9.2.5 Conclusion on classification and labelling for environmental hazards

On the basis of the above information on chronic toxicity, bioaccumulation and rapid degradability, the following classification and labelling of dimethachlor is proposed:

Aquatic Acute 1 H400 (Very toxic to aquatic life); as the lowest $L(E)C_{50}$ is > 0.01 and < 0.1 mg/L the associated M-factor is 10.

Aquatic Chronic 1 H410 (Very toxic to aquatic life with long lasting effects); as the lowest chronic NOEC is between 0.001 and 0.01 mg/L the associated M-factor is 10.

2.9.3 Summary of effects on arthropods

Effects on bees

Table 100: Table of endpoints to assess risk from dimethachlor

Organism	Test item	Test type	Endpoints	Reference (author, date, Syngenta Ref)
Honey bee (*Apis mellifera*)	A5089F	Acute oral	48 h LD_{50} > 104.9 µg a.s./bee	***Schmitzer (2000) CGA17020/0574***
		Acute contact	48 h LD_{50} >100 µg a.s./bee	
	A5089H	Chronic Adult Toxicity	LDD_{50} = 48.2 µg consumed a.s./bee/day	***Ruhland (2016) A5089H_10331***
		Chronic larval toxicity	8 d NOED = 91.6 µg a.s./larva	***Kleebaum (2016) A5089H_10353***
Bumblebee (*Bombus terrestris*)	Dimethachlor	Acute oral	48 h LD_{50} > 382.7 µg a.s./bumblebee	***Schmidt (2019) CGA017020_10433***
		Acute contact	48 h LD_{50} > 400 µg a.s./bumblebee	

Effects on non-target arthropods other than bees

Table 101: Table of endpoints to assess risk from dimethachlor

Species	Test type	Test item	Endpoints	Reference (author, date, Syngenta File No.)
Aphidius rhopalosiphi	Tier I glass plates	A5089F	LR_{50} = 181.4 mL product/ha	***Grimm (2000) CGA17020/0571***
	Tier II plant (3D)	A5089F	LR_{50} >6400 mL product/ha ER_{50} >6400 mL product/ha	***Moll (2001) CGA17020/0580***
Typhlodromus pyri	Tier I glass plates	A5089F	LR_{50} = 1305 mL product/ha NOER = 375 mL product/ha	***Reber (2000) CGA17020/0577***
	Tier II leaf disks (2D)	A5089F	LR_{50} >3000 mL product/ha ER_{50} >3000 mL product/ha	***Vinall (2003) CGA17020/0621***
Chrysoperla carnea	Tier II (2D) glass plates	A5089F	LR_{50} >3000 mL product/ha	***Grimm (2000) CGA17020/0570***
Pardosa spp.	Tier II (2D) quartz sand	A5089F	LR_{50} >3000 mL product/ha ER_{50} (feeding) >3000 mL product/ha	***Rohlig (2000) CGA17020/0565***

2.9.4 Summary of effects on non-target soil meso- and macrofauna

Earthworms

Table 102: Table of endpoints to assess risk from dimethachlor

Organism	Test item	Test type	Endpoints (mg/kg dry soil)	Reference (author, date, Syngenta Ref)
Earthworm (*Eisenia fetida*)	A5089H	Chronic toxicity	Fecundity $NOEC_{corr}$ = 61.5 (equivalent to 29 mg a.s./kg dw)[a]	***Dickinson (2015) A5089H_10325***
	CGA354742		EC_{10} = 158.2	***Définod (2016) CGA354742_10000***
	CGA369873		EC_{10} = 201.6	***Définod (2016) CGA369873/10013***
	SYN547047		NOEC = 1000	***Définod (2016) SYN547047/10016***
	CGA50266		NOEC = 1000	***Définod (2016) CGA050266/10005***
	CGA102935		NOEC = 1000	***Définod (2016) CGA102935/10151***
	SYN530561		NOEC = 1000	***Définod (2016) SYN530561/10004***
	CGA42443		NOEC = 16.35	***Fraimout (2017) CGA042443/10017***

For substances with a log P_{OW} > 2, the endpoint was corrected by a factor of 2 (see EFSA Supporting Publication 2015:EN-924)
[a] derived from a test conducted with A5089H. Actual content of dimethachlor in the formulation was 47.2%

Soil meso and macrofauna (other than earthworms)

Table 103: Table of endpoints to assess risk from dimethachlor

Organism	Test item	Endpoints (mg/kg dry soil)	Reference (author, date, Syngenta Ref)
Folsomia candida	A5089H	$NOEC_{corr}$ (fecundity): 18.5 (equivalent to 8.73 mg a.s./kg dw) [a]	***Dickinson (2015) A5089H_10323***
	CGA354742	NOEC (fecundity): 1000	***Définod (2016) GA354742_10002***
	CGA369873	EC_{10} (fecundity): 293.516	***Définod (2016) CGA369873_10012***
	SYN547047	NOEC (fecundity): 1000	***Définod (2016) SYN547047_10019***
	CGA50266	NOEC (fecundity): 555.6	***Définod (2016) CGA050266_10006***
	CGA102935	EC_{10} (fecundity): 27.2	***Définod (2016) CGA102935_10150***
	SYN530561	EC_{10} (fecundity): 152.037	***Définod (2016) SYN530561_10005***
	CGA42443	EC_{10} (fecundity): 24.28	***Définod (2017) CGA042443_10013***
Hypoaspis aculeifer	A5089H	EC_{10corr} (fecundity): 137.3 (equivalent to 64.8 mg a.s./kg dw) [a]	***Ramsden (2015) A5089H/10312***
	CGA354742	EC_{10} (fecundity): 66.985	***Deslandes (2016) CGA354742_10003***
	CGA369873	EC_{10} (fecundity): 15.835	***Définod (2016) CGA369873_10011***
	SYN547047	EC_{10} (fecundity): 16.236	***Définod (2016) SYN547047_10018***
	CGA50266	NOEC (fecundity) 16.35	***Définod (2016) CGA050266_10007***

Organism	Test item	Endpoints (mg/kg dry soil)	Reference (author, date, Syngenta Ref)
	CGA102935	NOEC (fecundity): 29.42	***Définod (2016) CGA102935_10152***
	SYN530561	EC_{10} (fecundity): 85.903	***Deslandes (2016) SYN530561_10008***
	CGA42443	NOEC (fecundity): 555.6	***Fraimout (2017) CGA042443_10011***

[a] derived from a test conducted with A5089H. Actual content of dimethachlor in the formulation was 47.2%

2.9.5 Summary of effects on soil nitrogen transformation

Table 104: Summary of toxicity endpoints for soil microorganisms

Test Type	Test Item	Endpoint (mg/kg)	Reference (author, date, Smartdoc Ref)
Nitrogen/Carbon Transformation	A5089F	NOEC = 21.08	***Völkel (2000) CGA17020/0552***
	Dimethachlor	NOEC = 10	***Caley (1994) CGA17020/0290***
	CGA354742	NOEC = 2.02	***Völkel (2001) CGA50266/0019***
	CGA369873	NOEC = 5	***Deslandes (2016) CGA369873_10014***
	SYN547047	NOEC = 5	***Deslandes (2016) SYN547047_10020***
	CGA50266	NOEC = 3.79	***Völkel (2001) CGA50266/0019***
	CGA102935	NOEC = 5	***Deslandes (2016) CGA102935_10153***
	SYN530561	NOEC = 5	***Deslandes (2016) SYN530561_10007***
	CGA42443	NOEC = 5	***Couture (2017) CGA042443/10015***

Values in **bold** are used in the risk assessment

2.9.6 Summary of effects on terrestrial non-target higher plants

Table 105: Summary of toxicity endpoints for non-target terrestrial plants

Species	Substance	Exposure System	Results	Reference
Echinochloa crus-galli	A5089F	21d Seedling Emergence	ER_{50} plant height = 42.0 g a.s./ha	Porch (2002) CGA17020/0609
Glycine max d [1)] *Raphanus sativus* d [2)] *Avena sativa* m [3)] *Lycopersicon esculentum* d [4)] *Allium cepa* m [5)] *Beta vulgaris* d [6)]	A5089F	21 d vegetative vigour	[1)] ER_{50} plant biomass = >1500 g a.s./ha [2)] ER_{50} plant biomass = >1500 g a.s./ha [3)] ER_{50} plant biomass = >1500 g a.s./ha [4)] ER_{50} plant biomass = >1500 g a.s./ha [5)] ER_{50} plant biomass = >1500 g a.s./ha [6)] ER_{50} plant biomass = >1500 g a.s./ha	Porch (2002) CGA17020/0608
Digitaria sanguinalis m *Setaria faberi* m *Sinapsis arvensis* d *Gallium aparine* d *Stellaria media* d *Kochia scoparia* d	CGA354742	Screening	Pre-emergence treatment with CGA354742 at 1000 g/ha caused minor effects of <50 % on *Kochia scoparia,* but no other species. Post-emergence applications at rates of 1000 g/ha did not have any effects on the species tested.	Spatz (2005) CGA50266/0002

Species	Substance	Exposure System	Results	Reference
Zea mays m *Hordeum vulgare* m *Triticum aestivum* m *Oryza sativa* m *Glycine max* d *Gossypium sp.* d *Brassica napus* d *Beta vulgaris* d *Alopecurus myosuroides* m *Avena fatua* m *Bromus tectorum* m *Lolium perenne* m *Setaria faberi* m *Panicum dichotomilflorum* m *Sorghum bicolor* m *Digitaria sanguinalis* m *Echinochloa crus-galli* m *Brachiaria plantaginea* m *Rottboellia exaltata* m *Cyperus esculentus* m *Euphorbia heterophylla* d *Sida spinose* d *Abutilon theophrasti* d *Xanthium canadense* d *Ipomoea purpurea* d *Amaranthus retroflexus* d *Chenopodium album* d *Polygonum convolvulus* d *Kochia scoparia* d *Sinapis arvensis* d *Stellaria media* d *Galium aparine* d *Veronica persica* d	CGA354742	Screening	In the pre-emergent test CGA354742 had slight effects on *Hordeum vulgare*, *Avena fatua* and *Kochia scoparia* at 2000 g a.s./ha and on *Kochia scoparia* at 1000 g a.s./ha. In the post-emergent test CGA354742 had no effects on any species tested at all applications rates, including 2000 g a.s./ha. CGA354742 was classified as having no herbicidal activity at relevant application rates.	Kerber (1995) CGA354742/0002
Digitaria sanguinalis m *Setaria faberi* m *Sinapsis arvensis* d *Gallium aparine* d *Stellaria media* d *Kochia scoparia* d	CGA373464	Screening	Pre-emergence treatment with CGA373464 at 1000 g/ha caused minor effects of <50 % in *Setaria faberi* and *Sinapsis arvensis.* Post-emergence applications of 1000 g/ha caused minor effects of <50 % on *Galium aparine*.	Spatz (2005) CGA50266/0002
Digitaria sanguinalis m *Setaria faberi* m *Sinapsis arvensis* d *Gallium aparine* d *Stellaria media* d *Kochia scoparia* d	CGA369873	Screening	Pre and post-emergence applications of CGA369873 at rates up to and including 1000 g/ha did not have any adverse effect on the species tested.	Spatz (2005) CGA50266/0002
Digitaria sanguinalis m *Setaria faberi* m *Sinapis arvensis* d *Ipomoea purpurea* d *Stellaria media* d *Kochia childsii* d	SYN547047	Screening	SYN547047 showed no phytotoxic effects on seedling emergence of all six plant species up to and including the application rate of 1000 g/ha, the highest rate tested. For vegetative vigour, SYN547047 showed phytotoxic effects on *Setaria faberi* at 1000 g/ha, but not on any of the other species tested.	Stefanut (2013) CGA017020_10015
Digitaria sanguinalis m *Setaria faberi* m *Sinapsis arvensis* d *Gallium aparine* d *Stellaria media* d *Kochia scoparia* d	CGA50266	Screening	Pre and post-emergence applications of CGA50266 at rates up to and including 1000 g/ha did not have any adverse effect on the species tested.	Spatz (2005) CGA50266/0002

Species	Substance	Exposure System	Results	Reference
Zea mays m *Hordeum vulgare* m *Triticum aestivum* m *Oryza sativa* m *Glycine max* d *Gossypium sp.* d *Brassica napus* d *Beta vulgaris* d *Alopecurus myosuroides* m *Avena fatua* m *Bromus tectorum* m *Lolium perenne* m *Setaria faberi* m *Panicum dichotomilflorum* m *Sorghum bicolor* m *Digitaria sanguinalis* m *Echinochloa crus-galli* m *Brachiaria plantaginea* m *Rottboellia exaltata* m *Cyperus esculentus* m *Euphorbia heterophylla* d *Sida spinose* d *Abutilon theophrasti* d *Xanthium canadense* d *Ipomoea purpurea* d *Amaranthus retroflexus* d *Chenopodium album* d *Polygonum convolvulus* d *Kochia scoparia* d *Sinapis arvensis* d *Stellaria media* d *Galium aparine* d *Veronica persica* d	CGA50266	Screening	In the pre-emergent test CGA50266 had no demonstrated herbicidal activity to any of the species tested. In the post-emergent test, the highest phytotoxicity score was 6 for the rate of 2000 g/ha for the species *Euphorbia heterophylla*, *Abutilon theophrasti* and *Xanthium canadense*.	Kerber (1995) CGA50266/0005
Allium cepa m *Avena sativa* m *Glycine max* d *Beta vulgaris* d *Brassica napus* d *Cucumis sativus* d	CGA102935	Screening	No significant effects were observed on seedling emergence and vegetative vigour of all six plant species up to and including the application rate of 1000 g CGA102935/ha.	Tomoroga (2009) CGA102935_10136
Digitaria sanguinalis m *Setaria faberi* m *Sinapis arvensis* d *Ipomoea purpurea* d *Stellaria media* d *Kochia childsii* d	CGA102935	Screening	No significant effects were observed on seedling emergence and vegetative vigour of all six plant species up to and including the application rate of 1000 g CGA102935/ha.	Tomoroga (2011) CGA102935_10145
Digitaria sanguinalis m *Setaria faberi* m *Sinapsis arvensis* d *Gallium aparine* d *Stellaria media* d *Kochia scoparia* d	SYN530561	Screening	Pre-emergence treatment with SYN530561 at ≥250 g/ha caused minor effects of <50 % on *Sinapsis arvensis,* but no other species. Post-emergence applications of SYN530561 at rates of 1000 g/ha did not have any effects on the species tested.	Spatz (2005) CGA50266/0002
Allium cepa m *Avena sativa* m *Glycine max* d *Beta vulgaris* d *Brassica napus* d *Cucumis sativus* d	CGA42443	Screening	No significant effects were observed on seedling emergence and vegetative vigour of all six plant species up to and including the application rate of 1000 g CGA42443/ha.	Tomoroga (2009) CGA042443_10002

Species	Substance	Exposure System	Results	Reference
Digitaria sanguinalis $_m$ *Setaria faberi* $_m$ *Sinapis arvensis* $_d$ *Ipomoea purpurea* $_d$ *Stellaria media* $_d$ *Kochia childsii* $_d$	CGA42443	Screening	No significant effects were observed on seedling emergence and vegetative vigour of all six plant species up to and including the application rate of 1000 g CGA42443/ha.	Tomoroga (2011) CGA102935_10145

m: monocotyledonous; *d*: dicotyledonous

Table 106: Endpoint used for the risk assessment non-target terrestrial plants

Test Substance	Test species	Lowest ER_{50}
A5089F	*Echinochloa crus-galli* (Seedling emergence)	42.0 (g a.s./ha)
	All species (Vegetative vigour)	>1500 (g a.s./ha)

2.9.7 Summary of effects on other terrestrial organisms (flora and fauna)

No further data on other terrestrial organisms are required.

2.9.8 Summary of effects on biological methods for sewage treatment

Table 107: Table of endpoints

Test item	Test species	Test type	Endpoints (mg a.s./L)		Reference (author, date, Syngenta File No.)
Dimethachlor (CGA17020)	Activated Sludge	Activated sludge respiration inhibition	EU	EC_{50} >100	***Weinstock (1994) CGA17020/0238***

2.9.9 Summary of product exposure and risk assessment

Birds
The risk assessment was performed in accordance with the '**EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)**[21]**.** For details of the risk assessment please refer to the Volume 3 – B.9 (CP).

Screening step
Acute risk assessment

Table 108: Screening step - Acute risk (TER_A) to birds from dimethachlor

Compound	Crop group	Indicator species	LD_{50} (mg/kg bw)	App. Rate (kg/ha)	DDD (mg/kg bw)	TER_A
Dimethachlor	Bare soil	Small granivorous bird	524	1	24.7	21
	Oilseed rape	Small omnivorous bird		1	159	**3.3**
	Bare soil	Small granivorous bird		0.75	18.5	28.3
	Oilseed rape	Small omnivorous bird		0.75	119	**4.4**

The TER_A values for small granivorous birds foraging on bare soil (oilseed rape pre-emergence) are greater than the Commission Regulation (EU) No. 546/2011 trigger of 10, indicating that acute risk to this guild of birds is acceptable. However, for birds foraging in oilseed rape (BBCH 10 - 20), the TER_A values are below the trigger, indicating that a Tier 1 risk assessment is required.

[21]European Food Safety Authority; Guidance Document on Risk Assessment for Birds and Mammals on request from EFSA. EFSA journal 2009; 7(12):1438. [139 pp.]

Table 109: Tier 1 - Acute risk (TER_A) to birds from dimethachlor

Compound	Crop grouping / growth stage	Generic focal species	Short cut value (mg/kg bw)	App. Rate (kg/ha)	DDD (mg/kg bw)	TER_A
Dimethachlor	BBCH 10-19	Medium herbivorous/granivorous bird "pigeon"	55.6	1	55.6	**9.4**
	BBCH 20-39	Medium herbivorous/granivorous bird "pigeon"	4.0	1	4.00	131
	BBCH 10-19	Small insectivorous bird "wagtail"	10.9	1	10.9	48
	BBCH 20-39	Small insectivorous bird "wagtail"	7.7	1	7.70	68
	BBCH 10-19	Large herbivorous bird "goose"	39.0	1	39.0	13.4
	BBCH 10-29	Small omnivorous bird "lark"	24.0	1	24.0	22
	BBCH 10-19	Medium herbivorous/granivorous bird "pigeon"	55.6	0.75	41.7	12.6
	BBCH 20-39	Medium herbivorous/granivorous bird "pigeon"	4.0	0.75	3.00	175
	BBCH 10-19	Small insectivorous bird "wagtail"	10.9	0.75	8.18	64
	BBCH 20-39	Small insectivorous bird "wagtail"	7.7	0.75	5.78	90.6
	BBCH 10-19	Large herbivorous bird "goose"	39.0	0.75	29.3	17.9
	BBCH 10-29	Small omnivorous bird "lark"	24.0	0.75	17.9	29

The Tier 1 TER_A value for the medium granivorous/omnivorous bird (pigeon) foraging between BBCH 10-19 in the crop treated with 1000 g dimethachlor/ha is below the trigger value, hence further consideration is necessary. A refinement is presented below.

Higher tier risk assessment for the acute risk of dimethachlor to medium granivorous bird/ pigeon following application of A5089H at 2 L/ha

Focal species selection

The EFSA Guidance Document on Birds and Mammals Risk Assessment (2009)[22] mentions the wood pigeon (*Columba palumbus*) as representative species for the medium granivorous/herbivorous birds in oilseed rape fields at BBCH 10 – 19. Wood pigeons are known as potential pest species to oilseed rape (Inglis *et al*. 1989; NA_14887) and oilseed rape is the preferred winter food for wood pigeons (Inglis *et al*. 1996; NA_14888). Both studies are summarised in Volume 3 – B.9 (CP). According to Prosser (2010)[23], the 90th percentile consumer PT value for wood pigeons in oilseed rape in winter is 0.68, indicating that this crop at early growth stage is an attractive foraging habitat. In the Guidance Document for Birds and Mammals risk assessment for the Northern zone[24], the wood pigeon is recognised as relevant focal species for winter oilseed rape fields at BBCH 10 – 29.

[22] European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals on request from EFSA. EFSA Journal 2009; 7(12): 1438. Doi:10.2903/j.efsa.2009.1438

[23] Prosser (2010). Consolidation of bird and mammal PT data for the use in risk assessment. Food and Environmental Research Agency, March 2010.

[24] Pesticide risk assessment for birds and mammals. Selection of relevant species and development of standard scenarios for higher tier risk assessment in the Northern Zone in accordance with Regulation EC 1107/2009. March 2018, version 1.6

Based on this information the Notifier deems it to be justified to use the wood pigeon as relevant focal species for the refined risk assessment of the medium granivorous/herbivorous bird "pigeon" in winter oilseed rape field at BBCH 10 – 19.

PD refinement wood pigeon

The EFSA Guidance Document on Birds and Mammals Risk Assessment (2009)[22] assumes that the diet of wood pigeon feeding in oilseed rape fields at BBCH 10 – 19 consists 100% crop leaves. However, it is known that a variety of seeds normally contribute significantly to the diet of wood pigeons. The Northern Guidance Document proposes PD values for the wood pigeon based on publicly available data and proposes the diet compositions for wood pigeons for risk assessments for winter oilseed rape at BBCH 10 – 29. PD values presented in the table below will be used for the refined risk assessment for the wood pigeon in early growth stages of oilseed rape. As a pragmatic approach, large seeds were assigned to food category "cereal seeds" and small seeds to food category "weed seeds".

Table 110: Estimated diet composition of woodpigeons feeding in oilseed rape (expert judgement based on EFSA 2009) as detailed in the Northern Guidance Document 2018 version 1.6.

Winter oilseed rape, BBCH 10-29	
Food category	**PD (fresh weight)**
Non-grass weeds & leafy crops	0.80
Large seeds	0.10
Small seeds	0.10

Using the diet compositions as described in the table above the FIR[25]/bw for wood pigeons in winter oilseed rape would be 0.275 (see calculations below) using the default body weight for the wood pigeon (490 g) as proposed in the EFSA Guidance Document for Birds and mammals Risk Assessment (2009)[26] as well as pigeon specific assimilation efficiencies as listed in Appendix G of the same document. These values will be used for the risk assessment.

Table 111: FIR calculation wood pigeon winter oilseed rape (BBCH 10-19)

Food type	**Energetic content of food** (kJ/g wet wt)	**Assimilation efficiency** (%)	**Energetic content of food, weighted by assimilation efficiency** (kJ/g wet wt)	**Proportion of different food items in diet mix** (% of diet wet weight)	**Energy uptake per gram of each diet item** [c] (kJ/g wet wt)	**DEE** (kJ)	**FIR Daily food consumption of different food items** (g wet wt/day)
Dicot leaves	1.31	53	0.69	80	0.56	-	107.65
Weed seeds	19.55	76	14.86	10	1.49	-	13.46
Cereal seeds	15.70	76	11.93	10	1.19	-	13.46
Total	-	-	-	100	3.23	435.25	134.56

Table 112: Higher tier acute risk assessment for wood pigeon in winter oilseed rape (BBCH 10-19, 1 kg

[25] Food intake rate

[26] European Food Safety Authority; Guidance Document on Risk Assessment for Birds and Mammals on request from EFSA. EFSA journal 2009; 7(12):1438. [139 pp.]

dimethachlor/ha)

Food type in diet	RUD	FIR/bw	App. rate (kg a.s./ha)	Proportion of diet (%)	DDD (mg a.s/kg bw/day)	LD_{50} (mg a.s./kg bw)	TER_A
Dicot leaves	70.3	0.275	1	80	15.47	524	26
Weed seeds	87		1	10	2.39		
Cereal seeds	87		1	10	2.39		
Total					20.25		

The higher tier TER_A value is above the Commission Regulation (EU) No. 546/2011 trigger of 10, indicating an acceptable risk to birds following an application of 1 kg dimethachlor/ha in oilseed rape at BBCH stage 10-19.

Long-term risk assessment

Table 113: Screening step – long – term (TER_{LT}) to birds from dimethachlor

Compound	Crop group	Indicator species	$LD_{50}/10$ (mg/kg bw/day)	App. Rate (kg/ha)	DDD (mg/kg bw/d)	TER_{LT}
Dimethachlor	Bare soil	Small granivorous bird	52.4	1	6.04	8.7
	Oilseed rape	Small omnivorous bird		1	34.34	**1.5**
	Bare soil	Small granivorous bird		0.75	4.53	11.6
	Oilseed rape	Small omnivorous bird		0.75	25.78	**2.0**

The TER_{LT} values for small granivorous birds foraging on bare soil (oilseed rape pre-emergence) is greater than the Commission Regulation (EU) No. 546/2011 trigger of 5, indicating that long-term risk to this guild of birds is acceptable. However, for birds foraging in oilseed rape, the TER_{LT} is below the trigger value, indicating that a Tier 1 risk assessment is required.

Tier 1 risk assessment

Table 114: Tier 1 – long – term (TER_{LT}) to birds from dimethachlor

Compound	Crop grouping / growth stage	Generic focal species	$LD_{50}/10$ (mg/kg bw/day)	App. rate (kg/ha)	DDD (mg/kg bw/d)	TER_{LT}
Dimethachlor	BBCH 10-19	Medium herbivorous/granivorous bird "pigeon"	52.4	1	12.0	**4.4**
	BBCH 20-39	Medium herbivorous/granivorous bird "pigeon"		1	1.86	28.2
	BBCH 10-19	Small insectivorous bird "wagtail"		1	3.13	16.7
	BBCH 20-39	Small insectivorous bird "wagtail"		1	1.48	35.4
	BBCH 10-19	Large herbivorous bird "goose"		1	8.43	6.2
	BBCH 10-29	Small omnivorous bird "lark"		1	5.78	9.1
	BBCH 10-19	Medium herbivorous/granivorous bird "pigeon"		0.75	9.02	5.8
	BBCH 20-39	Medium herbivorous/granivorous bird "pigeon"		0.75	1.39	37.7
	BBCH 10-19	Small insectivorous bird "wagtail"		0.75	2.35	22.3
	BBCH 20-39	Small insectivorous bird "wagtail"		0.75	1.11	47.2
	BBCH 10-19	Large herbivorous bird "goose"		0.75	6.32	8.3
	BBCH 10-29	Small omnivorous bird "lark"		0.75	4.33	12.1

At application rate 750 g a.s./ha, the TER_{LT} values are greater than the Commission Regulation (EU) No. 546/2011 trigger of 5, indicating that long-term risk to birds is acceptable following use of A5089H according to the proposed use patterns.
For the application rate of 1000 g a.s./ha the TER_{LT} values are greater than the Commission Regulation (EU) No. 546/2011 trigger of 5 with the exception of the medium herbivorous bird ‘pigeon’ which was below the TER_{LT} and will be considered further.

Higher tier long-term risk assessment for medium granivorous bird/pigeon exposed to dimethachlor following application of A5089H at 2 L/ha

The higher tier risk assessment for the medium granivorous/herbivorous bird “pigeon” is based on the following refinements:

1. Focal species justification
2. PD refinement
3. Foliage residue dissipation rate of dimethachlor
4. PT refinement

For details on refinement points 1 and 2 (focal species justification and PD refinement) please refer to the higher tier acute risk assessments for birds. More details on refinement point 3 (Foliage residue dissipation data) and 4 (PT refinement) are presented below.

Foliage residue dissipation rate of dimethachlor

Four independent foliage residue dissipation trials were carried out in Northern France, Germany and the United Kingdom (North 2017; A5089H_10374). The trials were carried out in spring sown oilseed rape. One application of A5089H was done at an application rate of 2 L/ha (equivalent to 1.0 kg a.s./ha) at BBCH stage 12-20. Following the application, treated oilseed rape whole plant samples were collected at 0 (<1 hour),1 hour, 2 hours, 4 hours, 6 hours, 24 hours, 48 hours and 96 hours after application (HAA) except for one trial where the 96 HAA sample was collected at 72 HAA in error.

Untreated oilseed rape whole plant samples were collected from within the trial plot area at 0 days before application (0 DBA). Samples were analysed for dimethachlor and its major plant metabolite SYN550004. The study is summarised in Volume 3 – B.9 (CP).

DT_{50} values for dimethachlor in oilseed rape foliage were calculated using CAKE version 3.3 (Kragten, 2019; CGA017020_10338). Dimethachlor declines rapidly in foliage with a DT_{50} value = 0.0383 days (geometric mean) following a SFO model. Based on this refined DT_{50} value the F_{TWA} for the refined long-term risk assessment for birds is 0.002631. This value will be used for the refined risk assessment. An overview of the results is presented in Table 115.

Table 115: Foliar DT_{50} calculations for dimethachlor in oilseed rape (Kragten, 2019)

Residue trial	**S16-02373-01**	**S16-02373-02**	**S16-02373-03**	**S16-02373-03**
Kinetic Model	SFO	SFO	SFO	SFO
Visual fit	Good	Acceptable	Good	Good
$\chi 2$ error (%)	12.0	20.3	11.3	9.85
Prob <0.05	0.0000367	0.001303	0.0000665	0.0000059
DT_{50} (days)	0.0298	0.0647	0.0643	0.0173

PT refinement wood pigeon

Prosser (2010[27]) summarised PT data for wood pigeon in oilseed rape available from England. PT data are not available per BBCH stage, but are available per season (spring, summer, autumn, winter). For winter oilseed rape, BBCH stage 10-19 is most likely to be reached in autumn (September – November). PT data were based on 27 individuals, of which 11 were considered 'consumer'. The 90th percentile PT (consumers only) for wood pigeons in oilseed rape in autumn was 0.29. In winter, however, oilseed rape fields were used more by wood pigeons (PT consumer only = 0.68; n = 8). In order to guarantee a conservative approach, the PT value for winter (0.68) will be used for the risk assessment.

[27] Prosser (2010). Consolidation of bird and mammal PT data for the use in risk assessment. Food and Environmental Research Agency, March 2010.

Table 116: PT data for wood pigeon in oilseed rape from England (Prosser, 2010)

Season	Crop	No. of birds - All birds	No. of birds - Consumer only	90th percentile PT (95% CLs) – All birds	90th percentile PT (95% CLs) – All birds	95th percentile PT (95% CLs) – Consumers only	95th percentile PT (95% CLs) – Consumers only
Autumn (September - November)	Oilseed rape	27	11	0.17	0.26	0.29	0.37
Winter (December – February)	Oilseed rape	15	8	0.59	0.68	0.68	0.75

In summary, the long-term risk to birds will be refined using the following refinements:

1. Focal species wood pigeon (490 g body weight)
2. PD wood pigeon

Table 117: Estimated diet composition of woodpigeons feeding in oilseed rape (expert judgement based on EFSA 2009) as detailed in the Northern Guidance Document 2018 version 1.6.

Winter oilseed rape, BBCH 10-29	
Food category	**PD (fresh weight)**
Non-grass weeds & leafy crops	0.80
Large seeds	0.10
Small seeds	0.10

3. DT_{50} dimethachlor on foliage: 0.0383 d
4. PT wood pigeon in oilseed rape = 0.68

The refined long-term risk assessment to birds is presented below.

Table 118: Higher tier long-term risk assessment for wood pigeon in winter rape (BBCH 10-19, 1 kg dimethachlor/ha)

Food type in diet	RUD	FIR/bw	App. rate (kg a.s./ha)	Proportion of diet (%)	F_{TWA}	PT	DDD (mg a.s/kg bw/day)	$LD_{50}/10$ (mg a.s./kg bw/d)	TER_{LT}
Dicot leaves	28.7	0.275	1	0.80	0.002631	0.68	0.01	52.4	64.53
Weed seeds	40.2		1	0.10	0.53		0.40		
Cereal seeds	40.2		1	0.10	0.53		0.40		
Total	-		-	-	-	-	0.81		

The higher tier TER_{LT} value is above the Commission Regulation (EU) No. 546/2011 trigger of 5, indicating an acceptable risk to birds following an application of 1 kg dimethachlor/ha in oilseed rape at BBCH stage 10-19.

Risk assessment for SYN550004

As described in Volume 3 – B.7 (CA) SYN550004 is formed at > 10% (46.8%) of parent level in foliage in plant metabolism studies, hence this needs to be considered in the avian risk assessment. Avian studies have not been conducted with this metabolite, but a mammalian test has been conducted and the LD_{50} was >2000 mg/kg bw (SYN550004_10000, summarised in Volume 3 – B.6 (CA)). Hence it is not anticipated that SYN550004 would not be more toxic to birds than the parent. Also, given that it is formed as a fraction of the parent (46.8%), the theoretical

maximum exposure to birds would be a maximum of 654 g/ha (based on an application rate of 1000 g dimethachlor/ha and the molecular weights of 255.8 g/mol and 357.4 for dimethachlor and SYN550004, respectively. In conclusion, the risk assessment for the parent covers the risk for SYN550004.

Risk assessment to birds through drinking water

For exposure via drinking water, the puddle scenario is relevant for the proposed use. The ratio of the effective application rate to the relevant acute and long-term toxicity endpoints is below the threshold value of 50 indicating that further assessment to birds from drinking water from puddles, is not required for dimethachlor.

Effects of secondary poisoning

According to **EFSA Guidance Document on Risk Assessment for Birds and Mammals, 2009**[28], substances with a log P_{OW} greater than 3 have potential for bioaccumulation. Dimethachlor has a log P_{OW} of 2.17 indicating a low risk of bioaccumulation through secondary poisoning. Therefore, based on the low log P_{OW} value the risk from bioaccumulation to fish-eating and worm-eating birds is not required.

For the soil metabolites considered for ecotoxicological risk assessment, CGA354742, SYN547047, CGA102935 maximum log P_{OW} values are -2.1, -2.0 and -3.0, respectively and for the soil/aquatic metabolites considered for ecotoxicological risk assessment, CGA50266 and CGA42443, the log P_{OW} values were estimated to be 1.43 and 1.87, respectively. Hence secondary poisoning risk assessment are not required for the metabolites of dimethachlor.

Mammals

The risk assessment was performed in accordance with the '**EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)**[29]**.** For details of the risk assessment please refer to the relevant Volume 3 – B.9 (CP).

Acute

Screening step

Table 119: Screening step - Acute risk (TER_A) to mammals from dimethachlor

Compound	Crop group	Indicator species	LD_{50} (mg/kg bw)	App. Rate (kg/ha)	DDD (mg/kg bw)	TER_A
Dimethachlor	Bare soil (Oilseed rape pre-emergence)	Small granivorous mammal	1600	1	14.4	111
	Oilseed rape (BBCH 10 – 20)	Small herbivorous mammal		1	118.4	13.51
	Bare soil (Oilseed rape pre-emergence)	Small granivorous mammal		0.75	10.8	148.15
	Oilseed rape (BBCH 10 – 20)	Small herbivorous mammal		0.75	88.8	18
SYN550004	Bare soil (Oilseed rape pre-emergence)	Small granivorous mammal	>2000	0.654	9.42	212.37
	Oilseed rape (BBCH 10 – 20)	Small herbivorous mammal		0.654	77.4	26

[28] European Food Safety Authority; Guidance Document on Risk Assessment for Birds and Mammals on request from EFSA. EFSA journal 2009; 7(12):1438. [139 pp.]
[29]European Food Safety Authority; Guidance Document on Risk Assessment for Birds and Mammals on request from EFSA. EFSA journal 2009; 7(12):1438. [139 pp.]

	Bare soil (Oilseed rape pre-emergence)	Small granivorous mammal		0.49	7.06	283.45
	Oilseed rape (BBCH 10 – 20)	Small herbivorous mammal		0.49	58.0	34.47

The TER_A values are all greater than the Regulation (EU) 546/2011 trigger of 10, indicating that acute risk to mammals is acceptable for dimethachlor and the dietary metabolite SYN550004 following use of A5089H according to the proposed use patterns.

Long-term

Screening step

Table 120: Screening step – long-term (TER_{LT}) to mammals from dimethachlor

Compound	Crop group	Indicator species	NOEL (mg/kg bw/d)	DDD (mg/kg bw/d)	App. Rate (kg/ha)	TER_{LT}
Dimethachlor	Bare soil (Oilseed rape pre-emergence)	Small granivorous mammal	20	3.50	1	5.7
	Oilseed rape (BBCH 10 – 20)	Small herbivorous mammal		25.60	1	**0.78**
	Bare soil (Oilseed rape pre-emergence)	Small granivorous mammal		2.62	0.75	7.6
	Oilseed rape (BBC 10 – 20)	Small herbivorous mammal		19.20	0.75	**1.04**

The TER_{LT} values for small granivorous mammals foraging on bare soil are greater than the Commission Regulation (EU) No. 546/2011 trigger of 10, indicating that chronic risk to this guild of mammals is acceptable. However, for herbivorous mammals foraging in newly emerged oilseed rape, the TER_{LT} values are below the trigger, indicating that a Tier 1 risk assessment is required.

Tier 1 risk assessment

The Tier 1 TER_{LT} values calculated for dimethachlor are given in the table below.

Table 121: Tier 1 – long-term (TER_{LT}) to mammals from dimethachlor

Compound	Crop grouping / growth stage	Generic focal species	NOEL (mg/kg bw/d)	App. rate (kg/ha)	DDD (mg/kg bw/d)	TER_{LT}
Dimethachlor	All season	Large herbivorous mammal 'lagomorph'	20	1	7.58	**2.64**
	BBCH 10-19	Small insectivorous mammal 'shrew'		1	2.23	9.0
	BBCH >20	Small insectivorous mammal 'shrew'		1	1.01	20
	BBCH 10-29	Small omnivorous mammal 'mouse'		1	4.13	**4.84**
	All season	Large herbivorous mammal 'lagomorph'		0.75	5.68	**3.52**

	BBCH 10-19	Small insectivorous mammal 'shrew'		0.75	1.67	12
	BBCH >20	Small insectivorous mammal 'shrew'		0.75	0.76	26.48
	BBCH 10-29	Small omnivorous mammal 'mouse'		0.75	3.10	6.5

For three scenarios (lagomorph feeding on oilseed rape after application at 1.0 and 0.75 kg a.s/ha, and mouse feeding on oilseed rape between BBCH 10-29 after application at 1 kg a.s./ha), the TER_{LT} values are below the Annex VI trigger value of 5. Therefore, further consideration is required.

Risk assessment refinement for long-term risk to mammals

The long-term risk assessment for the large herbivorous mammal "lagomorph" and small omnivorous mammal "mouse" scenarios will be refined using foliage residue dissipation data for dimethachlor in oilseed rape (North 2017 (A5089H_10374), please refer to the avian risk assessment for further details). Based on four foliage dissipation trials in spring oilseed rape in central Europe a foliar DT_{50} of 0.00383 days (geometric mean) was calculated (Kragten, 2019; CGA017020_10338), resulting in an F_{TWA} value of 0.002631 which will be used for the refined risk assessment. A summary of both studies can be found in Volume 3 – B.9 (CP).

Table 122: Refined long-term risk assessment small omnivorous mammal "mouse" dimethachlor oilseed rape (1 x 1000g/ha) BBCH 10-19

Food type in diet	RUD	FIR/bw	App. rate (kg a.s./ha)	Proportion of diet	F_{TWA}	DDD (mg a.s/kg bw/day)	NOAEL (mg a.s./kg bw/d)	TER_{LT}
Dicot leaves	28.7	0.271	1	0.25	0.002631	0.01	20	6.31
Weed seeds	40.2			0.50	0.53	2.89		
Arthropods	7.5			0.25	0.53	0.27		
Total	-	-	-	-	-	3.17		

Table 123: Refined long-term risk assessment large herbivorous mammal "lagomorph" dimethachlor oilseed rape (1 x 1000g/ha) BBCH 10-20

Food type in diet	RUD	FIR/bw	App. rate (kg a.s./ha)	Proportion of diet	F_{TWA}	DDD (mg a.s/kg bw/day)	NOAEL (mg a.s./kg bw/d)	TER_{LT}
Crop leaves	28.7	0.5	1	1.0	0.002631	0.038	20	526

Table 124: Refined long-term risk assessment large herbivorous mammal "lagomorph" dimethachlor oilseed rape (1 x 750/ha) BBCH 10-20

Food type in diet	RUD	FIR/bw	App. rate (kg a.s./ha)	Proportion of diet	F_{TWA}	DDD (mg a.s/kg bw/day)	NOAEL (mg a.s./kg bw/d)	TER_{LT}
Crop leaves	28.7	0.5	0.75	1.0	0.002631	0.028	20	714

Based on the refined long-term risk assessment, an acceptable long-term risk to mammals can be concluded following application of A5089H in oilseed rape according to the proposed use pattern.

Risk assessment for SYN550004

As described in the metabolite section, SYN550004 is formed at > 10% (46.8%) of parent level in foliage in residue studies, hence this needs to be considered in the mammalian risk assessment. An LD_{50} of >2000 mg/kg bw was derived form an acute study on rat (SYN550004_10000, summarised in Volume 3 – B.6 (CA)) and an acceptable risk was concluded. It is assumed that the long-term toxicity to mammals would not be any greater than for parent. Also,

given that it is formed as a fraction of the parent (46.8%), the theoretical maximum exposure to mammals would be a maximum of 654 g/ha (based on an application rate of 1000 g dimethachlor/ha and the molecular weights of 255.8 g/mol and 357.4 for dimethachlor and SYN550004, respectively. In conclusion, the long-term risk assessment for the parent would cover the risk for SYN550004.

Risk assessment to mammals through drinking water

For exposure via drinking water, the puddle scenario is relevant for the proposed use. The ratio of the effective application rate to the relevant acute and long-term toxicity endpoints is below the threshold value of 50 indicating that further assessment to mammals from drinking water from puddles, is not required for dimethachlor.

Effects of secondary poisoning

According to **EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009)**[30] substances with a log P_{OW} greater than 3 have potential for bioaccumulation. Dimethachlor has a log P_{OW} of 2.17 indicating a low risk of bioaccumulation through secondary poisoning. Therefore, based on the low log P_{OW} values, the risk from bioaccumulation to fish-eating and worm-eating mammals is not required.

For the soil metabolites CGA354742, SYN547047, CGA102935 considered for ecotoxicological risk assessment maximum log P_{OW} values are -2.1, -2.0 and -3.0, respectively and for the soil/aquatic metabolites considered for ecotoxicological risk assessment CGA50266 and CGA42443, the log P_{OW} values were estimated to be 1.43 and 1.87, respectively. Hence secondary poisoning risk assessment are not required for the metabolites of dimethachlor.

Aquatic organisms

The evaluation of the risk for aquatic organisms was performed in accordance with the recommendations of the "**EFSA (2013) Guidance document on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters** in the context of Regulation (EC) No 1107/2009", as provided by the Commission Services (SANTE-2015-00080, 15 January 2015). CGA354742, CGA373464, CGA369873, SYN547047, CGA50266, CGA102935, SYN530561 and CGA42443. For details of the risk assessment please refer to the relevant Volume 3 – B.9 (CP), Annex Point 10.2.

A5089H

Table 125: Risk assessment for A5089H for winter and spring oilseed rape (2106 g A5089H/ha)

Drift buffer [m]	Nozzle reduction [%]	Drift rate [%]	Initial $_{PECSW}$ (µg A5089H/L)	Fish acute RAC = 95 µg/L	Invertebrate acute RAC = 181 µg/L	Invertebrate chronic RAC = 100 µg/L	Algae RAC = 3.4 µg/L	Macrophyte RAC = 4.8 µg/L
				PEC/RAC ratio				
1	**-**	**2.77**	**19.4**	0.20	0.11	0.19	**5.7**	**4.0**
5	**-**	**0.57**	**4.00**	**-**	**-**	**-**	**1.2**	0.83
10	**-**	**0.29**	**2.04**	**-**	**-**	**-**	0.60	0.43
20	**-**	**0.15**	**1.05**	**-**	**-**	**-**	0.31	0.22
1	**50**	**1.39**	**9.72**	**-**	**-**	**-**	**2.9**	**2.0**
1	**75**	**0.69**	**4.86**	**-**	**-**	**-**	**1.4**	1.0
1	**90**	**0.28**	**1.94**	**-**	**-**	**-**	0.57	0.40

Values in bold are above the trigger value of 1

For the acute toxicity to fish and the acute and chronic toxicity to invertebrates the PEC/RAC is below 1 without additional mitigation, hence indicating an acceptable risk for these risk assessments. For algae, mitigation of either a 10 m drift buffer or 90% drift reduction technology is required to achieve an acceptable risk. For macrophytes, mitigation of either a 5 m drift buffer or 75% drift reduction technology is required to achieve an acceptable risk.

[30] European Food Safety Authority; Guidance Document on Risk Assessment for Birds and Mammals on request from EFSA. EFSA journal 2009; 7(12):1438. [139 pp.]

Table 126: Risk assessment for A5089H for winter and spring oilseed rape (1579.5 g A5089H/ha)

Drift buffer [m]	**Nozzle reduction [%]**	**Drift rate [%]**	**Initial $_{PECSW}$ (µg A5089H/L)**	**Fish acute RAC = 95 µg/L**	**Invertebrate acute RAC = 181 µg/L**	**Invertebrate chronic RAC = 100 µg/L**	**Algae RAC = 3.4 µg/L**	**Macrophyte RAC = 4.8 µg/L**
				PEC/RAC ratio				
1	**-**	**2.77**	**14.6**	0.15	0.081	0.15	**4.3**	**3.4**
5	**-**	**0.57**	**3.00**	**-**	**-**	**-**	0.88	0.62
10	**-**	**0.29**	**1.53**	**-**	**-**	**-**	0.45	0.32
20	**-**	**0.15**	**0.790**	**-**	**-**	**-**	0.23	0.16
1	**50**	**1.39**	**7.29**	**-**	**-**	**-**	**2.1**	**1.5**
1	**75**	**0.69**	**3.65**	**-**	**-**	**-**	**1.1**	0.76
1	**90**	**0.28**	**1.46**	**-**	**-**	**-**	0.43	0.30

Values in bold are above the trigger value of 1

For the acute toxicity to fish and the acute and chronic toxicity to invertebrates the PEC/RAC is below 1 without additional mitigation, hence indicating an acceptable risk for these risk assessments. For algae, mitigation of either a 5 m drift buffer or 90% drift reduction technology is required to achieve an acceptable risk. For macrophytes, mitigation of either a 5 m drift buffer or 75% drift reduction technology is required to achieve an acceptable risk.

Table 127: Tier 1 risk assessment for dimethachlor based on FOCUS Steps 1, 2 and 3 PECs for winter oilseed rape (1 × 1000 g a.s./ha) – BBCH 00

Group			**Fish - acute**	**Fish - chronic**	**Invertebrate - acute**	**Invertebrate - chronic**	**Algae**	**Macrophyte**	**Group**	**Sediment dweller - chronic**
Tier 1 RAC (µg/L)			**59**	**92**	**240**	**218**	**1.7[a]**	**6.58**	**Tier 1 RAC (µg/kg)**	**1560 µg/kg**
FOCUS Scenario		**PEC_{sw} (µg/L)**	**PEC/RAC (pelagic species)**						**PECsed (µg/kg)**	**PEC/RAC (benthic species)**
Step 1	-	316	**5.35**	**3.4**	**1.3**	**1.4**	**185.9**	**48**	202	0.13
Step 2	N EU	113.8	**1.93**	**1.2**	0.47	0.52	**67**	**17**	-	-
	S EU	92.7	**1.57**	**1.01**	0.39	0.43	**54.5**	**14**	-	-
Step 3	D2 Ditch	64.7	**1.09**	0.70	-	-	**38**	**9.8**	-	-
	D2 Stream	43.6	0.74	0.47	-	-	**25.65**	**6.6**	-	-
	D3 Ditch	6.41	0.11	0.070	-	-	**3.77**	0.97	-	-
	D4 Pond	0.462	0.008	0.0050	-	-	0.27	0.070	-	-
	D4 Stream	5.48	0.09	0.060	-	-	**3.22**	0.83	-	-
	D5 Pond	0.362	0.0061	0.0039	-	-	0.21	0.055	-	-
	D5 Stream	5.91	0.1	0.064	-	-	**3.48**	0.90	-	-
	R1 Pond	0.219	0.0037	0.0024	-	-	0.13	0.033	-	-
	R1 Stream	4.19	0.07	0.046	-	-	**2.46**	0.64	-	-
	R3 Stream	10.2	0.17	0.11	-	-	**6.0**	**1.6**	-	-

Values in bold are above the trigger value of 1 and hence further consideration is needed for these taxa/scenario combinations

[a] the lowest endpoint for algae is from study with formulation A5089H

An acceptable risk to sediment dwellers is identified using FOCUS Step 1 values, for invertebrates an acceptable risk is identified using FOCUS Step 2 values, and for fish (chronic) an acceptable risk is identified using FOCUS Step 3 values. For fish (acute) an unacceptable risk was identified at FOCUS Step 3, scenarios D2 ditch, for algae and macrophytes, an unacceptable risk was identified at FOCUS Step 3, scenarios D2 ditch, D2 stream and R3 stream. Additionaly, for algae unacceptable risk was identified at FOCUS Step 3 for scenarios D3 ditch, D4 stream, D5 stream and R1 stream. For all other scenarios an acceptable risk was identified at FOCUS Step 3. A higher tier risk assessment has therefore been conducted for those scenarios where the RAC/PEC value was >1.

Table 128: Tier 1 risk assessment for dimethachlor based on FOCUS Steps 1, 2 and 3 PECs for winter oilseed rape (1 × 1000 g a.s./ha) – BBCH 20

Group			**Fish - acute**	**Fish - chronic**	**Invertebrate - acute**	**Invertebrate - chronic**	**Algae**	**Macrophyte**	**Group**	**Sediment dweller - chronic**
Tier 1 RAC (µg/L)			**59**	**92**	**240**	**218**	**1.7[a]**	**6.58**	**Tier 1 RAC (µg/kg)**	**1560 µg/kg**
FOCUS Scenario		**PEC_{sw} (µg/L)**	**PEC/RAC (pelagic species)**						**PECsed (µg/kg)**	**PEC/RAC (benthic species)**
Step 1	-	316	**5.6**	**3.4**	**1.3**	**1.4**	**185.9**	**48**	202	0.13
Step 2	N EU	40.2	0.68	0.44	0.17	0.18	**23.65**	**6.1**	-	-
	S EU	33.9	0.57	0.37	0.14	0.16	**19.94**	**5.2**	-	-
Step 3	D2 Ditch	104	-	-	-	-	**61.18**	**16**	-	-
	D2 Stream	64.7	-	-	-	-	**38.06**	**9.8**	-	-
	D3 Ditch	6.37	-	-	-	-	**3.75**	0.97	-	-
	D4 Pond	0.839	-	-	-	-	0.49	0.13	-	-
	D4 Stream	5.48	-	-	-	-	**3.22**	0.83	-	-
	D5 Pond	1.10	-	-	-	-	0.65	0.17	-	-
	D5 Stream	5.91	-	-	-	-	**3.48**	0.90	-	-
	R1 Pond	0.219	-	-	-	-	0.13	0.033	-	-
	R1 Stream	4.19	-	-	-	-	**2.46**	0.64	-	-
	R3 Stream	21.1	-	-		-	**12.41**	**3.2**	-	-

Values in bold are above the trigger value of 1 and hence further consideration is needed for these taxa/scenario combinations

[a] the lowest endpoint for algae is from study with formulation A5089H

An acceptable risk to sediment dwellers is identified using FOCUS Step 1 values. For fish and invertebrates an acceptable risk is identified using FOCUS Step 2 values. For algae and macrophytes, an unacceptable risk was identified at FOCUS Step 3, scenarios D2 ditch, D2 stream and R3 stream. Additionaly, for algae unacceptable risk was identified at FOCUS Step 3 for scenarios D3 ditch, D4 stream, D5 stream and R1 stream. For all other scenarios an acceptable risk was identified at FOCUS Step 3. A higher tier risk assessment has therefore been conducted.

Table 129: Tier 1 risk assessment for dimethachlor based on FOCUS Steps 1, 2 and 3 PECs for winter oilseed rape (1 × 750 g a.s./ha) – BBCH 00

Group			**Fish - acute**	**Fish - chronic**	**Invertebrate - acute**	**Invertebrate - chronic**	**Algae**	**Macrophyte**	**Group**	**Sediment dweller - chronic**
Tier 1 RAC (µg/L)			**59**	**92**	**240**	**218**	**1.7[a]**	**6.58**	**Tier 1 RAC (µg/kg)**	**1560 µg/kg**
FOCUS Scenario		**PECsw (µg/L)**	**PEC/RAC (pelagic species)**						**PECsed (µg/kg)**	**PEC/RAC (benthic species)**
Step 1	-	237	**4.0**	**2.6**	0.99	**1.0**	**139.41**	**36**	152	0.097
Step 2	N EU	85.3	**1.46**	0.93	0.36	0.37	**50.18**	**13**	-	-
	S EU	69.6	**1.18**	0.78	0.29	0.30	**40.94**	**11**	-	-
Step 3	D2 Ditch	43.9	0.74	-	-	-	**25.82**	**6.7**	-	-
	D2 Stream	29.7	0.50	-	-	-	**17.47**	**4.5**	-	-
	D3 Ditch	4.81	0.08	-	-	-	0.67	0.73	-	-
	D4 Pond	0.344	0.006	-	-	-	0.048	0.052	-	-
	D4 Stream	4.11	0.069	-	-	-	0.57	0.63	-	-
	D5 Pond	0.267	0.045	-	-	-	0.037	0.041	-	-
	D5 Stream	4.44	0.075	-	-	-	0.62	0.69	-	-
	R1 Pond	0.164	0.0027	-	-	-	0.023	0.025	-	-
	R1 Stream	3.14	0.053	-	-	-	0.44	0.048	-	-
	R3 Stream	7.68	0.13	-	-	-	**4.52**	**1.2**	-	-

Values in bold are above the trigger value of 1 and hence further consideration is needed for these taxa/scenario combinations

[a] the lowest endpoint for algae is from study with formulation A5089H

An acceptable risk to sediment dwellers and invertebrates (acute) is identified using FOCUS Step 1 values. For invertebrates (chronic) and fish (chronic) an acceptable risk is identified using FOCUS Step 2 values. For algae and macrophytes, an unacceptable risk was identified at FOCUS Step 3, scenario D2 ditch, D2 stream and R3 stream. For all other scenarios an acceptable risk was identified at FOCUS Step 3. A higher tier risk assessment has therefore been conducted.

Table 130: Tier 1 risk assessment for dimethachlor based on FOCUS Steps 1, 2 and 3 PECs for winter oilseed rape (1 × 750 g a.s./ha) – BBCH 20

Group			**Fish - acute**	**Fish - chronic**	**Invertebrate - acute**	**Invertebrate - chronic**	**Algae**	**Macrophyte**	**Group**	**Sediment dweller - chronic**
Tier 1 RAC (µg/L)			**59**	**92**	**240**	**218**	**1.7[a]**	**6.58**	**Tier 1 RAC (µg/kg)**	**1560 µg/kg**
FOCUS Scenario		**PECsw (µg/L)**	**PEC/RAC (pelagic species)**						**PECsed (µg/kg)**	**PEC/RAC (benthic species)**
Step 1	-	237	**4.02**	**2.6**	0.99	**1.1**	**139.41**	**36**	152	0.097
Step 2	N EU	30.1	0.51	0.33	0.13	0.14	**17.71**	**4.6**	-	-
	S EU	25.4	0.43	0.28	0.11	0.12	**14.94**	**3.9**	-	-
Step 3	D2 Ditch	77.7	-	-	-	-	**45.71**	**12**	-	-
	D2 Stream	48.5	-	-	-	-	**28.53**	**7.4**	-	-
	D3 Ditch	4.77	-	-	-	-	**2.81**	0.73	-	-
	D4 Pond	0.624	-	-	-	-	0.37	0.095	-	-
	D4 Stream	4.11	-	-	-	-	**2.42**	0.63	-	-
	D5 Pond	0.792	-	-	-	-	0.47	0.12	-	-
	D5 Stream	4.44	-	-	-	-	**2.61**	0.68	-	-
	R1 Pond	0.164	-	-	-	-	0.10	0.025	-	-
	R1 Stream	3.14	-	-	-	-	**1.85**	0.48	-	-
	R3 Stream	15.9	-	-	-	-	**9.35**	**2.4**	-	-

Values in bold are above the trigger value of 1 and hence further consideration is needed for these taxa/scenario combinations

[a] the lowest endpoint for algae is from study with formulation A5089H

An acceptable risk to sediment dwellers and invertebrates (acute) is identified using FOCUS Step 1 values. For fish (acute and chronic) and invertebrates (chronic) an acceptable risk is identified using FOCUS Step 2 values. For algae and macrophytes, an unacceptable risk was identified at FOCUS Step 3, scenario D2 ditch, D2 stream and R3 stream. Additionaly, for algae unacceptable risk was identified at FOCUS Step 3 for scenarios D3 ditch, D4 stream, D5 stream and R1 stream. For all other scenarios an acceptable risk was identified at FOCUS Step 3. A higher tier risk assessment has therefore been conducted.

Table 131: Tier 1 risk assessment for dimethachlor based on FOCUS Steps 1, 2 and 3 PECs for spring oilseed rape (1 × 1000 g a.s./ha) – BBCH 00

Group			**Fish - acute**	**Fish - chronic**	**Invertebrate - acute**	**Invertebrate - chronic**	**Algae**	**Macrophyte**	**Group**	**Sediment dweller - chronic**
Tier 1 RAC (µg/L)			**59**	**92**	**240**	**218**	**1.7[a]**	**6.58**	**Tier 1 RAC (µg/kg)**	**1560 µg/kg**
FOCUS Scenario		**PECsw (µg/L)**	**PEC/RAC (pelagic species)**						**PECsed (µg/kg)**	**PEC/RAC (benthic species)**
Step 1	-	316	**5.36**	**3.4**	**1.3**	**1.4**	**185.88**	**48**	202	0.13
Step 2	N EU	114	**1.9**	**1.2**	0.48	0.52	**67.06**	**17**	-	-
	S EU	92.7	**1.57**	**1.01**	0.39	0.43	**54.53**	**14**	-	-
Step 3	D1 Ditch	6.64	0.11	0.072	-	-	**3.91**	**1.0**	-	-
	D1 Stream	5.27	0.089	0.057	-	-	**3.10**	0.80	-	-
	D3 Ditch	6.34	0.107	0.069	-	-	**3.73**	0.96	-	-
	D4 Pond	0.219	0.0037	0.0024	-	-	0.13	0.033	-	-
	D4 Stream	4.87	0.0825	0.053	-	-	**2.86**	0.74	-	-
	D5 Pond	0.219	0.0037	0.0024	-	-	0.13	0.033	-	-
	D5 Stream	5.02	0.0851	0.055	-	-	**2.95**	0.76	-	-
	R1 Pond	0.244	0.0041	0.0027	-	-	0.14	0.037	-	-
	R1 Stream	4.18	0.071	0.045	-	-	**2.46**	0.64	-	-

Values in bold are above the trigger value of 1 and hence further consideration is needed for these taxa/scenario combinations

[a] the lowest endpoint for algae is from study with formulation A5089H

An acceptable risk to sediment dwellers is identified using FOCUS Step 1 values. For invertebrates (acute and chronic) an acceptable risk is identified using FOCUS Step 2 values. For fish (acute and chronic) and macrophytes, an acceptable risk was identified at FOCUS Step 3, with the exception of the D1 ditch scenario for macrophytes. For algae unacceptable risk was identified at FOCUS Step 3 for scenarios D1 ditch, D1 stream, D3 ditch, D4 stream, D5 stream and R1 stream. A higher tier risk assessment has therefore been conducted.

Table 132: Tier 1 risk assessment for dimethachlor based on FOCUS Steps 1, 2 and 3 PECs for spring oilseed rape (1 × 750 g a.s./ha) – BBCH 00

Group			**Fish - acute**	**Fish - chronic**	**Invertebrate - acute**	**Invertebrate - chronic**	**Algae**	**Macrophyte**	**Group**	**Sediment dweller - chronic**
Tier 1 RAC (µg/L)			**59**	**92**	**240**	**218**	**1.7**[a]	**6.58**	**Tier 1 RAC (µg/kg)**	**1560 µg/kg**
FOCUS Scenario		**PECsw (µg/L)**	**PEC/RAC (pelagic species)**						**PECsed (µg/kg)**	**PEC/RAC (benthic species)**
Step 1	-	237	**4.0**	**2.6**	0.99	**1.1**	**139.41**	**36**	152	0.097
Step 2	N EU	85.3	**1.44**	0.93	0.36	0.39	**50.17**	**13**	-	-
	S EU	69.6	**1.8**	0.76	0.29	0.32	**40.94**	**11**	-	-
Step 3	D1 Ditch	4.98	0.08	-	-	-	**2.93**	0.76	-	-
	D1 Stream	3.95	0.067	-	-	-	**2.32**	0.60	-	-
	D3 Ditch	4.75	0.08	-	-	-	**2.79**	0.72	-	-
	D4 Pond	0.164	0.0028	-	-	-	0.096	0.025	-	-
	D4 Stream	3.65	0.0619	-	-	-	**2.15**	0.56	-	-
	D5 Pond	0.164	0.0028	-	-	-	0.096	0.025	-	-
	D5 Stream	3.77	0.0639	-	-	-	**2.22**	0.57	-	-
	R1 Pond	0.185	0.0031	-	-	-	0.11	0.028	-	-
	R1 Stream	3.13	0.053	-	-	-	**1.84**	0.48	-	-

Values in bold are above the trigger value of 1 and hence further consideration is needed for these taxa/scenario combinations

[a] the lowest endpoint for algae is from study with formulation A5089H

An acceptable risk to sediment dwellers and invertebrates (acute) is identified using FOCUS Step 1 values. For invertebrates (chronic) and fish (chronic) an acceptable risk is identified using FOCUS Step 2 values. For fish (acute) and macrophytes, an acceptable risk was identified at FOCUS Step 3. For algae unacceptable risk was identified at FOCUS Step 3 for scenarios D1 ditch, D1 stream, D3 ditch, D4 stream, D5 stream and R1 stream. A higher tier risk assessment has therefore been conducted.

Refinement of the acute risk to fish

The Tier 1 risk assessment indicated a potential acute risk to fish following use of A5089H in winter oilseed rape only ((1 × 1000 g a.s./ha) – BBCH 00). The PEC/RAC ratio was above the trigger value of 1 at Step 3 for scenario D2 Ditch. Refinement is therefore required. Calculations were made PEC/RAC radios was calculated for Step 4 scenario D2 Ditch. There are two acute studies conducted with two different fish species rainbow ([redacted] (1993)) and common carp ([redacted] (1993)), therefore the geomean value of 6.7 µg a.s./L (RAC = 67) will be used in the risk assessment.

Table 133: Tier 1 risk assessment for dimethachlor based on FOCUS Steps 4 PECs for winter oilseed rape BBCH 00 (1 × 1000 g a.s./ha) D2 Ditch

Mitigation options			Application Rate 1x 1000 g a.s/ha	
No spray buffer (m)	Nozzle reduction (%)	Vegetative strip (m)	PEC (µg/L)	PEC/RAC ratio
5	-	-	64.7	0.96
10	-	-	64.7	0.96
20	-	-	64.7	0.96
-	50	-	64.7	0.96
-	75	-	64.7	0.96
-	90	-	64.7	0.96
10	-	10	64.7	0.96
20	-	20	64.7	0.96

Based on the refined risk assessment, PEC/RAC values are just below 1 for scenario Ditch D2, indicating acceptable risk for fish acute. Mitigation measures have no impact on the PEC value.

Refinement of the long-term risk to algae

For winter oilseed rape at both rates and both BBCH growth stages, the PEC/RAC ratio for was greater than 1 for the scenarios at Step 3. Hence a refined risk assessment is presented below. The refined risk assessment is based on two mesocosm studies conducted with A5089H (Arts et al. 2011; A5089H_10002; Cole & Vervliet-Scheebaum, 2011; A5089H_10004), including MDD analyses. Full study summaries of the actual mesocosm studies as well as the MDD reports (Stegger 2019; A5089H_10435; Stegger 2019; A5089H_10436) are given in Volume 3 - CP B.9 under point B.9.3.3.

Algae

Two higher tier mesocosm studies are available for dimethachlor, which provide information on community level effects and recovery in conditions more closely resembling edge-of-field surface waters. In accordance with the updated Aquatic Guidance Document (AGD; EFSA, 2013), post-hoc MDD analyses have been conducted in order to gauge the statistical power of these studies. These analyses have demonstrated that the experimental systems used in these studies contained an adequate (≥8) number of potentially sensitive taxa in MDD Category 1.

In the study by Arts *et al.* (2011; A5089H_10002) the lowest NOEC at community level based on PRC analysis was <1.0 µg a.s./L although responses were minor and transient and recovery was observed up to and including treatment level 30 µg a.s./L. For 12 of the 19 affected taxa, the lowest NOEC was ≥ 3.0 µg a.s./L. Two taxa showed a lowest NOEC of 1.0 µg a.s./L, while for five taxa the lowest NOEC was < 1.0 µg a.s.L. However, all affected taxa showed recovery up to and including treatment level 3.0 µg a.s./L. The majority of the taxa affected (i.e. 17 out of 19) also showed recovery at treatment levels up to and including 10 µg a.s./L. MDD analysis of the Arts study (Stegger 2019; A5089H_10436) showed that the most sensitive group were the algae, namely *Ankistrodesmus sp.*, which showed a pronounced short-term effect followed by recovery at 1.0 µg a.s./L, the lowest concentration tested (Effect Class 3A). For *Alona sp.* a significantly lower abundance compared to control could be observed on the last sampling day (day 82) down to the lowest concentration tested (Effect Class 2-4A). However, the occurrence of this apparent effect on abundance at the end of the study (82 days after first application) combined with the absence of a consistent concentration-response indicate that these differences were not treatment-related.

In the study by Cole and Vervliet-Scheebaum (2011), the NOEC for the most sensitive algal species (*Ankistrodesmus spiralis*) was 4.5 µg a.s./L. However, it should be noted that the abundance of this species was very low – constituting only 0.3% of the phytoplankton sampled from the control microcosms, and the species was not considered to be representative of the phytoplankton community in this study. MDD analysis of the Cole and Vervliet-Scheebaum study (Stegger 2019; A5089H_10435) showed again that algae were the most sensitive group. Some algal taxa show pronounced short-term effects followed by recovery in the lowest test concentration (4.5 µg a.s./L). The apparent

effect on *Ankistrodesmus spiralis* down to the lowest test concentration was not robust: this species was not present in any of the treatments at the start of the study, only appearing in very low abundances in control cosms from day 13. Considering the MDD analyses of the two available mesocosm studies with dimethachlor, a higher tier risk assessment for algae will be based on the recovery option, there being pronounced short-term effects followed by recovery down to the lowest test concentration concentration (1.0 µg/L) in the study by Arts *et al*. 2011 (A5089H_10002). In accordance with the aquatic Guidance Document, applying an assessment factor of 3 to this Effect Class 3A concentration provides an ERO-RAC of 0.33 µg a.s./L. An AF of 3 is justified considering the consistency of the data within and between two independent studies, which therefore reduces uncertainty in extrapolating the results to real edge-of-field surface waters.

Table 134: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of a no spray buffer for winter oilseed rape (1 × 1000 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	No spray buffer			5 m		10 m		20 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D2	ditch	Drainage	64.7	**196.1**	64.7	**196.1**	64.7	**196.1**
	D2	stream	Drainage	43.6	**132.1**	43.6	**132.1**	43.6	**132.1**
	D3	ditch	Drift / dry deposition	1.8	**5.5**	1.02	**3.1**	0.536	**1.6**
	D4	pond	Drainage	0.462	**1.4**	0.438	**1.3**	0.417	**1.3**
	D4	stream	Drift	2.01	**6.1**	1.07	**3.2**	0.559	**1.7**
	D5	pond	Drainage	0.358	**1.1**	0.298	0.9	0.298	0.9
	D5	stream	Drift	2.16	**6.5**	1.15	**3.5**	0.600	**1.8**
	R1	pond	Drift / dry deposition	0.214	0.6	0.155	0.5	0.102	0.3
	R1	stream	Drift	1.57	**4.8**	0.843	**2.6**	0.440	**1.3**
	R3	stream	Runoff	10.2	**30.0**	10.2	**30.0**	10.2	**30.0**
20	D2	ditch	Drainage	104	**315.2**	104	**315.2**	104	**315.2**
	D2	stream	Drainage	64.7	**196.1**	64.7	**196.1**	64.7	**196.1**
	D3	ditch	Drift / dry deposition	1.87	**5.7**	1.07	**3.2**	0.572	**1.7**
	D4	pond	Drainage	0.857	**2.6**	0.829	**2.5**	0.801	**2.4**
	D4	stream	Drift	2.07	**6.3**	1.13	**3.4**	0.943	**2.6**
	D5	pond	Drainage	1.10	**3.3**	1.10	**3.3**	1.10	**3.3**
	D5	stream	Drift	2.21	**6.7**	1.20	**3.6**	0.802	**2.4**
	R1	pond	Drift / dry deposition	0.260	0.8	0.190	0.6	0.122	0.4
	R1	stream	Drift	1.65	**5.0**	0.905	**2.7**	0.476	**1.4**
	R3	stream	Runoff	21.1	**63.9**	21.1	**63.9**	**21.1**	**63.9**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 135: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of a no spray buffer for winter oilseed rape (1 × 1000 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	Nozzle reduction			50%		75%		90%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D2	ditch	Drainage	64.7	**196.1**	64.7	**196.1**	64.7	**196.1**
	D2	stream	Drainage	43.6	**132.1**	43.6	**132.1**	43.6	**132.1**
	D3	ditch	Drift / dry deposition	3.3	**10.0**	1.75	**5.3**	0.837	**2.5**
	D4	pond	Drainage	0.433	**1.3**	0.413	**1.3**	0.401	**1.2**
	D4	stream	Drift	2.75	**8.3**	1.39	**4.2**	0.592	**1.8**
	D5	pond	Drainage	0.298	0.9	0.298	0.9	0.298	0.9
	D5	stream	Drift	2.96	**9.0**	1.50	**4.5**	0.632	**1.9**
	R1	pond	Drift / dry deposition	0.143	0.4	0.089	0.3	0.057	0.2
	R1	stream	Drift	2.14	**6.5**	1.10	**3.3**	0.478	**1.4**
	R3	stream	Runoff	10.2	**30.0**	10.2	**30.0**	10.2	**30.0**
20	D2	ditch	Drainage	104	**315.2**	104	**315.2**	104	**315.2**
	D2	stream	Drainage	64.7	**196.1**	64.7	**196.1**	64.7	**196.1**
	D3	ditch	Drift / dry deposition	3.26	**9.9**	1.84	**5.6**	1.03	**3.1**
	D4	pond	Drainage	0.833	**2.5**	0.811	**2.5**	0.798	**2.4**
	D4	stream	Drift	2.82	**8.5**	1.49	**4.5**	0.943	**2.9**
	D5	pond	Drainage	1.10	**3.3**	1.10	**3.3**	1.10	**3.3**
	D5	stream	Drift	3.01	**9.1**	1.59	**4.8**	0.802	**2.4**
	R1	pond	Drift / dry deposition	0.200	0.6	0.146	0.4	0.114	0.3
	R1	stream	Drift	2.24	**6.8**	1.20	**3.6**	0.580	**1.8**
	R3	stream	Runoff	21.1	**63.9**	21.1	**63.9**	21.1	**63.9**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 136: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of drift and runoff reduction for winter oilseed rape (1 × 1000 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	**Vegetative strip**			**10 m**		**20 m**	
	No spray buffer			**10 m**		**20 m**	
	Scenario	**Water body**	**Dominant route of entry**	**PEC_{sw} (µg/L)**	**PEC/ERO-RAC (0.33 µg/L)**	**PEC_{sw} (µg/L)**	**PEC/ERO-RAC (0.33 µg/L)**
00	D2	ditch	Drainage	64.7	**196.1**	64.7	**196.1**
	D2	stream	Drainage	43.6	**132.1**	43.6	**132.1**
	D3	ditch	Drift / dry deposition	1.02	**3.1**	0.536	**1.6**
	D4	pond	Drainage	0.438	**1.3**	0.417	**1.3**
	D4	stream	Drift	1.07	**3.2**	0.559	**1.7**
	D5	pond	Drainage	0.298	0.9	0.298	0.9
	D5	stream	Drift	1.15	**3.5**	0.600	**1.8**
	R1	pond	Drift / dry deposition	0.155	0.5	0.102	0.3
	R1	stream	Drift	0.843	**2.6**	0.440	**1.3**
	R3	stream	Runoff	4.65	**14.1**	2.44	**7.3**
20	D2	ditch	Drainage	104	**315.2**	104	**315.2**
	D2	stream	Drainage	64.7	**196.1**	64.7	**196.1**
	D3	ditch	Drift / dry deposition	1.07	**3.2**	0.572	**1.7**
	D4	pond	Drainage	0.829	**2.5**	0.801	**2.4**
	D4	stream	Drift	1.13	**3.4**	0.943	**2.9**
	D5	pond	Drainage	1.10	**3.3**	1.10	**3.3**
	D5	stream	Drift	1.20	**3.6**	0.802	**2.4**
	R1	pond	Drift / dry deposition	0.190	0.6	0.122	0.4
	R1	stream	Drift	0.905	**2.7**	0.476	**1.4**
	R3	stream	Runoff	9.6	**29.1**	5.03	**15.2**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 137: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of drift reducing nozzles and no-spray buffer zone for winter oilseed rape (1 × 1000 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	No spray buffer			5 m		10 m		20 m	
	Drift reducing nizzles			90%		75%		50%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D3	ditch	Drift / dry deposition	0.336	**1.0**	0.390	**1.2**	0.399	**1.2**
	D4	pond	Drainage	0.396	**1.2**	0.402	**1.2**	0.406	**1.2**
	D4	stream	Drift	0.431	**1.3**	0.431	**1.3**	0.431	**1.3**
	D5	pond	Drainage	0.298	0.9	0.298	0.9	0.298	0.9
	D5	stream	Drift	0.262	0.8	0.326	1.0	0.336	**1.0**
	R1	pond	Drift / dry deposition	0.045	0.1	0.060	0.2	0.071	0.2
	R1	stream	Drift	0.199	0.6	0.248	0.8	0.256	0.8
20	D3	ditch	Drift / dry deposition	0.288	0.9	0.332	1.0	0.339	**1.0**
	D4	pond	Drainage	0.770	**2.3**	0.776	**2.4**	0.781	**2.4**
	D4	stream	Drift	0.943	**2.9**	0.943	**2.9**	0.943	**2.9**
	D5	pond	Drainage	1.095	**3.3**	1.095	**3.3**	1.095	**3.3**
	D5	stream	Drift	0.802	**2.4**	0.802	**2.4**	0.802	**2.4**
	R1	pond	Drift / dry deposition	0.045	0.1	0.060	0.2	0.071	0.2
	R1	stream	Drift	0.316	1.0	0.316	1.0	0.316	1.0

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 138: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of a no spray buffer for winter oilseed rape (1 × 750 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	No spray buffer			5 m		10 m		20 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D2	ditch	Drainage	43.9	**133.0**	43.9	**133.0**	43.9	**133.0**
	D2	stream	Drainage	29.7	**90.0**	29.7	**90.0**	29.7	**90.0**
	D3	ditch	Drift / dry deposition	1.38	**4.18**	0.761	**2.3**	0.401	**1.2**
	D4	pond	Drainage	0.344	**1.04**	0.326	0.99	0.311	0.94
	D4	stream	Drift	1.510	**4.58**	0.806	**2.4**	0.419	**1.27**
	D5	pond	Drainage	0.264	0.8	0.219	0.66	0.216	0.65
	D5	stream	Drift	1.622	**4.9**	0.865	**2.6**	0.450	**1.36**
	R1	pond	Drift / dry deposition	0.161	0.5	0.116	0.35	0.076	0.23
	R1	stream	Drift	1.175	**3.56**	0.632	**1.9**	0.330	1.0
	R3	stream	Runoff	7.68	**23.27**	7.68	**23.27**	7.68	**23.27**
20	D2	ditch	Drainage	77.7	**235.45**	77.7	**235.45**	77.7	**235.5**
	D2	stream	Drainage	48.5	**147.0**	48.5	**147.0**	48.5	**147.0**
	D3	ditch	Drift / dry deposition	1.40	**4.24**	0.802	**2.4**	0.429	**1.3**
	D4	pond	Drainage	0.638	**1.93**	0.617	**1.9**	0.596	**1.8**
	D4	stream	Drift	1.55	**4.7**	0.845	**2.56**	0.701	**2.1**
	D5	pond	Drainage	0.792	**2.4**	0.792	**2.4**	0.792	**2.4**
	D5	stream	Drift	1.66	**5.0**	0.902	**2.73**	0.575	**1.7**
	R1	pond	Drift / dry deposition	0.195	0.6	0.143	0.43	0.091	0.3
	R1	stream	Drift	1.24	**3.8**	0.679	**2.06**	0.357	**1.1**
	R3	stream	Runoff	15.9	**48.2**	15.9	**48.2**	15.9	**48.2**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 139: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation nozzle reduction for winter oilseed rape (1 × 750 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	Nozzle reduction			50%		75%		90%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D2	ditch	Drainage	43.9	**133.0**	43.9	**133.0**	43.9	**133.0**
	D2	stream	Drainage	29.7	**90.0**	29.7	**90.0**	29.7	**90.0**
	D3	ditch	Drift / dry deposition	2.46	**7.5**	1.31	**4.0**	0.63	**1.9**
	D4	pond	Drainage	0.322	0.98	0.307	0.9	0.298	0.9
	D4	stream	Drift	2.07	**6.3**	1.04	**3.2**	0.444	**1.3**
	D5	pond	Drainage	0.216	0.7	0.216	0.7	0.216	0.7
	D5	stream	Drift	2.22	**6.7**	1.12	**3.4**	0.474	**1.4**
	R1	pond	Drift / dry deposition	0.107	0.3	0.067	0.2	0.043	0.1
	R1	stream	Drift	1.604	**4.9**	0.826	**2.5**	0.359	**1.1**
	R3	stream	Runoff	7.68	**23.3**	7.68	**23.3**	7.68	**23.3**
20	D2	ditch	Drainage	77.7	**235.5**	77.7	**235.5**	77.7	**235.5**
	D2	stream	Drainage	48.5	**147.0**	48.5	**147.0**	48.5	**147.0**
	D3	ditch	Drift / dry deposition	2.44	**7.4**	1.38	**4.2**	0.772	**2.3**
	D4	pond	Drainage	0.620	**1.9**	0.603	**1.8**	0.594	**1.8**
	D4	stream	Drift	2.11	**6.4**	1.12	**3.4**	0.701	**2.1**
	D5	pond	Drainage	0.792	**2.4**	0.792	**2.4**	0.792	**2.4**
	D5	stream	Drift	2.26	**6.8**	1.19	**3.6**	0.579	**1.8**
	R1	pond	Drift / dry deposition	0.150	0.5	0.110	0.3	0.086	0.3
	R1	stream	Drift	1.68	**5.1**	0.90	**2.7**	0.435	**1.3**
	R3	stream	Runoff	15.9	**48.2**	15.9	**48.2**	15.9	**48.2**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 140: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation with of drift and runoff reduction for winter oilseed rape (1 × 750 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	**Vegetative strip**			**10 m**		**20 m**	
	No spray buffer			**10 m**		**20 m**	
	Scenario	**Water body**	**Dominant route of entry**	**PEC_{sw} (µg/L)**	**PEC/ERO-RAC (0.33 µg/L)**	**PEC_{sw} (µg/L)**	**PEC/ERO-RAC (0.33 µg/L)**
00	D2	ditch	Drainage	43.9	**133.0**	43.9	**133.0**
	D2	stream	Drainage	29.7	**90.0**	29.7	**90.0**
	D3	ditch	Drift / dry deposition	0.761	**2.3**	0.401	**1.2**
	D4	pond	Drainage	0.326	0.99	0.311	0.9
	D4	stream	Drift	0.806	**2.4**	0.419	**1.3**
	D5	pond	Drainage	0.219	0.7	0.216	0.7
	D5	stream	Drift	0.865	**2.6**	0.450	**1.4**
	R1	pond	Drift / dry deposition	0.116	0.4	0.076	0.2
	R1	stream	Drift	0.632	**1.9**	0.330	1.0
	R3	stream	Runoff	3.5	**10.6**	1.83	**5.5**
20	D2	ditch	Drainage	77.7	**235.5**	77.7	**235.5**
	D2	stream	Drainage	48.5	**147.0**	48.5	**147.0**
	D3	ditch	Drift / dry deposition	0.802	**2.4**	0.429	**1.3**
	D4	pond	Drainage	0.617	**1.9**	0.596	**1.8**
	D4	stream	Drift	0.845	**2.6**	0.701	**2.1**
	D5	pond	Drainage	0.792	**2.4**	0.792	**2.4**
	D5	stream	Drift	0.902	**2.7**	0.575	**1.7**
	R1	pond	Drift / dry deposition	0.143	0.4	0.091	0.3
	R1	stream	Drift	0.679	**2.1**	0.357	**1.1**
	R3	stream	Runoff	7.23	**21.9**	3.79	**11.5**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 141: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation with of drift reducing nozzles and no-spray buffer zone for winter oilseed rape (1 × 750 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	**No spray buffer**			**5 m**		**10 m**		**20 m**	
	Drift reducing nozzles			**90%**		**75%**		**50%**	
	Scenario	**Water body**	**Dominant route of entry**	**PEC_{sw} (µg/L)**	**PEC/ERO-RAC (0.33 µg/L)**	**PEC_{sw} (µg/L)**	**PEC/ERO-RAC (0.33 µg/L)**	**PEC_{sw} (µg/L)**	**PEC/ERO-RAC (0.33 µg/L)**
00	D3	ditch	Drift / dry deposition	0.295	0.9	0.335	**1.0**	0.342	**1.0**
	D4	pond	Drainage	0.297	0.9	0.302	0.9	0.305	0.9
	D4	stream	Drift	0.321	1.0	0.321	1.0	0.321	1.0
	D5	pond	Drainage	0.216	0.7	0.216	0.7	0.216	0.7
	D5	stream	Drift	0.216	0.7	0.261	0.8	0.269	0.8
	R1	pond	Drift / dry deposition	0.041	0.1	0.052	0.2	0.060	0.2
	R1	stream	Drift	0.161	0.5	0.198	0.6	0.204	0.6
20	D3	ditch	Drift / dry deposition	0.254	0.8	0.287	0.9	0.292	0.9
	D4	pond	Drainage	0.576	**1.7**	0.580	**1.8**	0.583	**1.8**
	D4	stream	Drift	0.701	**2.1**	0.701	**2.1**	0.701	**2.1**
	D5	pond	Drainage	0.792	**2.4**	0.792	**2.4**	0.792	**2.4**
	D5	stream	Drift	0.575	**1.7**	0.575	**1.7**	0.575	**1.7**
	R1	pond	Drift / dry deposition	0.041	0.1	0.052	0.2	0.060	0.2
	R1	stream	Drift	0.246	0.7	0.246	0.7	0.246	0.7

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 142: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of a no spray buffer for spring oilseed rape (1 × 1000 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	No spray buffer			5 m		10 m		20 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D1	ditch	Drift	2.00	**6.1**	1.20	**3.6**	0.761	**2.3**
	D1	stream	Drift	2.06	**6.2**	1.18	**3.6**	0.693	**2.1**
	D3	ditch	Drift	1.72	**5.2**	0.911	**2.8**	0.474	**1.4**
	D4	pond	Drift / dry deposition	0.214	0.6	0.155	0.5	0.102	0.3
	D4	stream	Drift	1.80	**5.4**	0.959	**2.9**	0.499	**1.5**
	D5	pond	Drift / dry deposition	0.215	0.7	0.156	0.5	0.102	0.3
	D5	stream	Drift	1.85	**5.6**	0.986	**3.0**	0.513	**1.5**
	R1	pond	Runoff	0.244	0.7	0.196	0.6	0.153	0.5
	R1	stream	Runoff	1.70	**5.1**	1.70	**5.1**	1.70	**5.1**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 143: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of nozzle reduction for spring oilseed rape (1 × 1000 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	Nozzle reduction			50%		75%		90%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D1	ditch	Drift	3.46	**10.5**	1.88	**5.7**	1.02	**3.1**
	D1	stream	Drift	2.75	**8.3**	1.48	**4.5**	0.712	**2.2**
	D3	ditch	Drift	3.17	**9.6**	1.58	**4.8**	0.672	**2.0**
	D4	pond	Drift / dry deposition	0.143	0.4	0.089	0.3	0.057	0.2
	D4	stream	Drift	2.46	**7.5**	1.24	**3.8**	0.512	**1.6**
	D5	pond	Drift / dry deposition	0.143	0.4	0.090	0.3	0.058	0.2
	D5	stream	Drift	2.53	**7.7**	1.28	**3.9**	0.522	**1.6**
	R1	pond	Runoff	0.186	0.6	0.143	0.4	0.117	0.4
	R1	stream	Runoff	2.13	**6.5**	1.70	**5.1**	1.70	**5.1**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 144: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation with of drift and runoff reduction for spring oilseed rape (1 × 1000 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	Vegetative strip			10 m		20 m	
	No spray buffer			10 m		20 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D1	ditch	Drift	1.20	**3.6**	0.761	**2.3**
	D1	stream	Drift	1.18	**3.6**	0.693	**2.1**
	D3	ditch	Drift	0.911	**2.8**	0.474	**1.4**
	D4	pond	Drift / dry deposition	0.155	0.5	0.102	0.3
	D4	stream	Drift	0.959	**2.9**	0.499	**1.5**
	D5	pond	Drift / dry deposition	0.156	0.5	0.102	0.3
	D5	stream	Drift	0.986	**3.0**	0.513	**1.6**
	R1	pond	Runoff	0.155	0.5	0.102	0.3
	R1	stream	Runoff	0.836	**2.5**	0.436	**1.3**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 145: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of drift reducing nozzles and no-spray buffer zone for spring oilseed rape (1 × 1000 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	No spray buffer			5 m		10 m		20 m	
	Drift reducing nozzles			90%		75%		50%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D1	ditch	Drainage	0.575	**1.7**	0.622	**1.9**	0.630	**1.9**
	D1	stream	Drift	0.380	**1.2**	0.440	**1.3**	0.450	**1.4**
	D3	ditch	Drift	0.253	0.8	0.298	0.9	0.305	0.9
	D4	pond	Drift / dry deposition	0.045	0.1	0.060	0.2	0.071	0.2
	D4	stream	Drift	0.197	0.6	0.255	0.8	0.264	0.8
	D5	pond	Drift / dry deposition	0.046	0.1	0.061	0.2	0.072	0.2
	D5	stream	Drift	0.199	0.6	0.258	0.8	0.268	0.8
	R1	pond	Runoff	0.108	0.3	0.119	0.4	0.128	0.4
	R1	stream	Runoff	1.696	**5.1**	1.696	**5.1**	1.696	**5.1**

Table 146: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of a no spray buffer for spring oilseed rape (1 × 750 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	No spray buffer			5 m		10 m		20 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D1	ditch	Drift	1.49	**4.5**	0.896	**2.7**	0.565	**1.7**
	D1	stream	Drift	1.54	**4.7**	0.879	**2.7**	0.516	**1.6**
	D3	ditch	Drift	1.29	**3.9**	0.683	**2.1**	0.355	**1.1**
	D4	pond	Drift / dry deposition	0.161	0.5	0.117	0.4	0.076	0.2
	D4	stream	Drift	1.35	**4.1**	0.719	**2.2**	0.374	**1.1**
	D5	pond	Drift / dry deposition	0.161	0.5	0.117	0.4	0.077	0.2
	D5	stream	Drift	1.39	**4.2**	0.739	**2.2**	0.385	**1.2**
	R1	pond	Runoff	0.185	0.6	0.149	0.5	0.117	0.4
	R1	stream	Runoff	1.33	**4.0**	1.33	**4.0**	1.33	**4.0**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 147: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation of nozzle reduction for spring oilseed rape (1 × 750 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	Nozzle reduction			50%		75%		90%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D1	ditch	Drift	2.59	**7.8**	1.41	**4.3**	0.76	**2.3**
	D1	stream	Drift	2.06	**6.2**	1.10	**3.3**	0.53	**1.6**
	D3	ditch	Drift	2.38	**7.2**	1.19	**3.6**	0.50	**1.5**
	D4	pond	Drift / dry deposition	0.107	0.3	0.067	0.2	0.043	0.1
	D4	stream	Drift	1.84	**5.6**	0.932	**2.8**	0.384	**1.1**
	D5	pond	Drift / dry deposition	0.107	0.3	0.067	0.2	0.043	0.1
	D5	stream	Drift	1.90	**5.8**	0.957	**2.9**	0.392	**1.2**
	R1	pond	Runoff	0.142	0.4	0.110	0.3	0.090	0.3
	R1	stream	Runoff	1.60	**4.8**	1.33	**4.0**	1.33	**4.0**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 148: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation with of drift and runoff reduction for spring oilseed rape (1 × 750 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	Vegetative strip			10 m		20 m	
	No spray buffer			10 m		20 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D1	ditch	Drainage	0.896	**2.7**	0.565	**1.7**
	D1	stream	Drift	0.879	**2.7**	0.516	**1.6**
	D3	ditch	Drift	0.683	**2.1**	0.355	**1.1**
	D4	pond	Drift / dry deposition	0.117	0.4	0.076	0.2
	D4	stream	Drift	0.719	**2.2**	0.374	**1.1**
	D5	pond	Drift / dry deposition	0.117	0.4	0.077	0.2
	D5	stream	Drift	0.739	**2.2**	0.385	**1.2**
	R1	pond	Runoff	0.116	0.4	0.076	0.2
	R1	stream	Runoff	0.627	**1.9**	0.327	0.99

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 149: Higher tier risk assessment for algae for dimethachlor based on FOCUS Step 4 with mitigation with of drift reducing nozzles and no-spray buffer zone for spring oilseed rape (1 × 750 g a.s./ha) – Mesocosm ERO-RAC = 0.33 µg a.s./L

BBCH	No spray buffer			5 m		10 m		20 m	
	Drift reducing nozzles			90%		75%		50%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)	PEC_{sw} (µg/L)	PEC/ERO-RAC (0.33 µg/L)
00	D1	ditch	Drainage	0.465	**1.4**	0.501	**1.5**	0.506	**1.5**
	D1	stream	Drift	0.288	0.9	0.333	1.0	0.340	**1.0**
	D3	ditch	Drift	0.219	0.7	0.252	0.8	0.258	0.8
	D4	pond	Drift / dry deposition	0.041	0.1	0.052	0.2	0.060	0.2
	D4	stream	Drift	0.153	0.5	0.196	0.6	0.203	0.6
	D5	pond	Drift / dry deposition	0.041	0.1	0.052	0.2	0.060	0.2
	D5	stream	Drift	0.153	0.5	0.198	0.6	0.205	0.6
	R1	pond	Runoff	0.088	0.3	0.097	0.3	0.104	0.3
	R1	stream	Runoff	1.330	**4.0**	1.330	**4.0**	1.330	**4.0**

The tables above show that the risk for algae is unacceptable for the scenarios D2, D3, D4, D5 and R3 for the proposed use in winter oilseed rape, 1 × 1000 g a.s./ha, even with the use of risk mitigation measures (no spray buffer and drift reducing nozzles).
For the proposed use in winter oilseed rape, 1 × 750 g a.s./ha an unacceptable risk for algae is recognised for scenarios D2, D3 and R3 (BBCH 00) and for scenarios D2, D4, D5 and R3 (BBCH 20) even with the use of risk mitigation measures (no spray buffer and drift reducing nozzles).
For the proposed use in spring oilseed rape, 1 × 1000 g a.s./ha an unacceptable risk for algae is recognised for scenarios D1 and R1 (BBCH 00) even with the use of risk mitigation measures (no spray buffer and drift reducing nozzles).
For the proposed use in spring oilseed rape, 1 × 750 g a.s./ha an unacceptable risk for algae is recognised for scenarios D1 and R1 (BBCH 00) even with the use of risk mitigation measures (no spray buffer and drift reducing nozzles).

Table 150: Overview of safe uses with needed mitigation measures for dimethachlor uses in oilseed rape using ERO-RAC = 0.33 µg/L. FOCUS scenarios mentioned in the table pass the risk assessment using the mitigation measure mentioned.

Crop	**Use rate (g a.s./ha)**	**BBCH**	**Mitigation**				
			20 m non spray bufferzone	**20 m vegetated buffer strip**	**5 m non spray bufferzone + 90% drift reducing nozzles**	**10 m non spray bufferzone + 75% drift reducing nozzles**	**20 m non spray bufferzone + 50% drift reducing nozzles**
Winter oilseed rape	1000	Pre-emergence			D5, R1	D5, R1	R1
Winter oilseed rape	1000	Post- emergence			D3, R1	D3, R1	R1
Winter oilseed rape	750	Pre-emergence	R1	R1	D3, D4, D5, R1	D4, D5, R1	D4, D5, R1
Winter oilseed rape	750	Post- emergence			D3, R1	D3, R1	D3, R1
Spring oilseed rape	1000	Pre-emergence			D3, D4, D5	D3, D4, D5	D3, D4, D5
Spring oilseed rape	750	Pre-emergence		R1	D3, D4, D5	D3, D4, D5	D3, D4, D5

Refinement of the risk to aquatic macrophytes for winter and spring oilseed rape

Macrophytes

Two mesocosm studies with assessing the effects of dimethachlor on macrophytes are available.

In the study by Arts *et al.* 2011 (A5089H_10002) eight macrophyte species were tested. The most sensitive species was the emergent species, *Myosotis palustris*, which had a minimum NOEC value of 10 µg a.s./L. In corroboration, the MDD analysis of this study reported an Effect Class 2-4A (effect at the end of the study for which recovery could not be demonstrated) of 30 µg a.s./L for *Myosotis* total shoot length. Consequently, for this endpoint the highest Effect Class 1 was 10 µg a.s./L. Applying an assessment factor of 2 to this value provides an ETO-RAC for aquatic macrophytes of 5 µg a.s./L.

In the study by Cole and Vervliet-Scheebaum (2011; A5089H_10004) of the four macrophyte species tested the most sensitive species were *Elodea canadensis* and *Myriophyllum spicatum*, with minimum Day 84 NOEC values of 26.8 µg a.s./L. The MDD analysis of this study reported an Effect Class 3A of 26.8 µg a.s./L. for *Elodia* (main shoot length), which was the most sensitive macrophyte endpoint in this study. Consequently an ERO-RAC of 8.9 µg a.s./L. (26.8/AF 3), and an ETO-RAC of 2.25 (4.5/AF 2) can be derived from this study.

The risk assessment for algae clearly covers the risk to aquatic macrophytes.

Using the ETO-RAC of 2.25 µg a.s./L, all PEC/ETO-RAC values for macrophytes are below the trigger value of 1, with the exception of the D2 scenarios for uses in winter oilseed rape and the R3 scenario for uses in winter oilseed rape.

Table 151: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation of a no spray buffer for winter oilseed rape (1 × 1000 g a.s./ha) – Mesocosm RAC = 2.25

BBCH	No spray buffer			5 m		10 m		20 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ETO-RAC	PEC_{sw} (µg/L)	PEC/ETO-RAC	PEC_{sw} (µg/L)	PEC/ETO-RAC
00	D2	ditch	Drainage	64.7	**28.8**	64.7	**28.8**	64.7	**28.8**
	D2	stream	Drainage	43.6	**19.4**	43.6	**19.4**	43.6	**19.4**
	D3	ditch	Drift / dry deposition	1.8	0.8	1.02	0.5	0.536	0.2
	D4	pond	Drainage	0.462	0.2	0.438	0.2	0.417	0.2
	D4	stream	Drift	2.01	0.9	1.07	0.5	0.559	0.25
	D5	pond	Drainage	0.358	0.2	0.298	0.1	0.298	0.1
	D5	stream	Drift	2.16	1.0	1.15	0.5	0.600	0.3
	R1	pond	Drift / dry deposition	0.214	0.1	0.155	0.1	0.102	0.05
	R1	stream	Drift	1.57	0.7	0.843	0.4	0.440	0.2
	R3	stream	Runoff	10.2	**4.5**	10.2	**4.5**	10.2	**4.5**
20	D2	ditch	Drainage	104	**46.2**	104	**46.2**	104	**46.2**
	D2	stream	Drainage	64.7	**28.8**	64.7	**28.8**	64.7	**28.8**
	D3	ditch	Drift / dry deposition	1.87	0.8	1.07	0.5	0.572	0.25
	D4	pond	Drainage	0.857	0.4	0.829	0.4	0.801	0.36
	D4	stream	Drift	2.07	0.9	1.13	0.5	0.943	0.4
	D5	pond	Drainage	1.10	0.5	1.10	0.5	1.10	0.5
	D5	stream	Drift	2.21	1.0	1.20	0.5	0.802	0.36
	R1	pond	Drift / dry deposition	0.260	0.1	0.190	0.1	0.122	0.05
	R1	stream	Drift	1.65	0.7	0.905	0.4	0.476	0.2
	R3	stream	Runoff	21.1	**9.4**	21.1	**9.4**	21.1	**9.4**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 152: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation of nozzle reduction for winter oilseed rape (1 × 1000 g a.s./ha) – Mesocosm RAC = 2.25

BBCH	Nozzle reduction			50%		75%		90%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ETO-RAC	PEC_{sw} (µg/L)	PEC/ETO-RAC	PEC_{sw} (µg/L)	PEC/ETO-RAC
00	D2	ditch	Drainage	64.7	**28.8**	64.7	**28.8**	64.7	**28.8**
	D2	stream	Drainage	43.6	**19.4**	43.6	**19.4**	43.6	**19.4**
	D3	ditch	Drift / dry deposition	3.3	**1.5**	1.75	0.8	0.837	0.4
	D4	pond	Drainage	0.433	0.2	0.413	0.2	0.401	0.2
	D4	stream	Drift	2.75	**1.2**	1.39	0.6	0.592	0.26
	D5	pond	Drainage	0.298	0.1	0.298	0.1	0.298	0.1
	D5	stream	Drift	2.96	**1.3**	1.50	0.7	0.632	0.28
	R1	pond	Drift / dry deposition	0.143	0.06	0.089	0.04	0.057	0.03
	R1	stream	Drift	2.14	1.0	1.10	0.5	0.478	0.2
	R3	stream	Runoff	10.2	**4.5**	10.2	**4.5**	10.2	**4.5**
20	D2	ditch	Drainage	104	**46.2**	104	**46.2**	104	**46.2**
	D2	stream	Drainage	64.7	**28.8**	64.7	**28.8**	64.7	**28.8**
	D3	ditch	Drift / dry deposition	3.26	**1.4**	1.84	0.8	1.03	0.5
	D4	pond	Drainage	0.833	0.4	0.811	0.4	0.798	0.35
	D4	stream	Drift	2.82	**1.25**	1.49	0.7	0.943	0.4
	D5	pond	Drainage	1.10	0.5	1.10	0.5	1.10	0.5
	D5	stream	Drift	3.01	**1.3**	1.59	0.7	0.802	0.36
	R1	pond	Drift / dry deposition	0.200	0.1	0.146	0.06	0.114	0.05
	R1	stream	Drift	2.24	1.0	1.20	0.5	0.580	0.26
	R3	stream	Runoff	21.1	**9.4**	21.1	**9.4**	21.1	**9.4**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 153: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation of drift and runoff reduction for winter oilseed rape (1 × 1000 g a.s./ha) – Mesocosm RAC = 2.25

BBCH	Vegetative strip			10 m		20 m	
	No spray buffer			10 m		20 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ETO-RAC	PEC_{sw} (µg/L)	PEC/ETO-RAC
00	D2	ditch	Drainage	64.7	**28.8**	64.7	**28.8**
	D2	stream	Drainage	43.6	**19.4**	43.6	**19.4**
	D3	ditch	Drift / dry deposition	1.02	0.45	0.536	0.24
	D4	pond	Drainage	0.438	0.2	0.417	0.2
	D4	stream	Drift	1.07	0.5	0.559	0.25
	D5	pond	Drainage	0.298	0.1	0.298	0.1
	D5	stream	Drift	1.15	0.5	0.600	0.3
	R1	pond	Drift / dry deposition	0.155	0.07	0.102	0.05

	R1	stream	Drift	0.843	0.37	0.440	0.2
	R3	stream	Runoff	4.65	**2.07**	2.44	**1.08**
20	D2	ditch	Drainage	104	**46.2**	104	**46.2**
	D2	stream	Drainage	64.7	**28.8**	64.7	**28.8**
	D3	ditch	Drift / dry deposition	1.07	0.5	0.572	0.25
	D4	pond	Drainage	0.829	0.4	0.801	0.36
	D4	stream	Drift	1.13	0.5	0.943	0.4
	D5	pond	Drainage	1.10	0.5	1.10	0.5
	D5	stream	Drift	1.20	0.5	0.802	0.36
	R1	pond	Drift / dry deposition	0.190	0.08	0.122	0.05
	R1	stream	Drift	0.905	0.4	0.476	0.2
	R3	stream	Runoff	9.6	**4.3**	5.03	**2.2**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 154: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation of a no spray buffer for winter oilseed rape (1 × 750 g a.s./ha) - Mesocosm RAC = 2.25

BBCH	**No spray buffer**			**5 m**		**10 m**		**20 m**	
	Scenario	**Water body**	**Dominant route of entry**	**PEC_{sw} (µg/L)**	**PEC/ETO-RAC**	**PEC_{sw} (µg/L)**	**PEC/ETO-RAC**	**PEC_{sw} (µg/L)**	**PEC/ETO-RAC**
00	D2	ditch	Drainage	43.9	**19.5**	43.9	**19.5**	43.9	**19.5**
	D2	stream	Drainage	29.7	**13.2**	29.7	**13.2**	29.7	**13.2**
	D3	ditch	Drift / dry deposition	1.38	0.6	0.761	0.3	0.401	0.2
	D4	pond	Drainage	0.344	0.15	0.326	0.1	0.311	0.1
	D4	stream	Drift	1.510	0.7	0.806	0.36	0.419	0.2
	D5	pond	Drainage	0.264	0.1	0.219	0.1	0.216	0.1
	D5	stream	Drift	1.622	0.7	0.865	0.4	0.450	0.2
	R1	pond	Drift / dry deposition	0.161	0.07	0.116	0.05	0.076	0.03
	R1	stream	Drift	1.175	0.5	0.632	0.3	0.330	0.15
	R3	stream	Runoff	7.68	**3.4**	7.68	**3.4**	7.68	**3.4**
20	D2	ditch	Drainage	77.7	**34.5**	77.7	**34.5**	77.7	**34.5**
	D2	stream	Drainage	48.5	**21.6**	48.5	**21.56**	48.5	**21.6**
	D3	ditch	Drift / dry deposition	1.40	0.6	0.802	0.36	0.429	0.2
	D4	pond	Drainage	0.638	0.3	0.617	0.27	0.596	0.26
	D4	stream	Drift	1.55	0.7	0.845	0.4	0.701	0.3
	D5	pond	Drainage	0.792	0.35	0.792	0.35	0.792	0.35
	D5	stream	Drift	1.66	0.7	0.902	0.4	0.575	0.26
	R1	pond	Drift / dry deposition	0.195	0.1	0.143	0.06	0.091	0.04
	R1	stream	Drift	1.24	0.55	0.679	0.3	0.357	0.16
	R3	stream	Runoff	15.9	**7.1**	15.9	**7.1**	15.9	**7.1**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 155: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation of nozzle reduction for winter oilseed rape (1 × 750 g a.s./ha) – RAC = 2.25

BBCH	Nozzle reduction			50%		75%		90%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ETO-RAC	PEC_{sw} (µg/L)	PEC/ETO-RAC	PEC_{sw} (µg/L)	PEC/ETO-RAC
00	D2	ditch	Drainage	43.9	**19.5**	43.9	**19.5**	43.9	**19.5**
	D2	stream	Drainage	29.7	**13.2**	29.7	**13.2**	29.7	**13.2**
	D3	ditch	Drift / dry deposition	2.46	**1.1**	1.31	0.6	0.63	0.3
	D4	pond	Drainage	0.322	0.1	0.307	0.1	0.298	0.1
	D4	stream	Drift	2.07	0.9	1.04	0.46	0.444	0.2
	D5	pond	Drainage	0.216	0.1	0.216	0.1	0.216	0.1
	D5	stream	Drift	2.22	1.0	1.12	0.5	0.474	0.2
	R1	pond	Drift / dry deposition	0.107	0.05	0.067	0.03	0.043	0.02
	R1	stream	Drift	1.604	0.7	0.826	0.37	0.359	0.16
	R3	stream	Runoff	7.68	**3.4**	7.68	**3.4**	7.68	**3.4**
20	D2	ditch	Drainage	77.7	**34.5**	77.7	**34.5**	77.7	**34.5**
	D2	stream	Drainage	48.5	**21.6**	48.5	**21.6**	48.5	**21.6**
	D3	ditch	Drift / dry deposition	2.44	**1.1**	1.38	0.6	0.772	0.3
	D4	pond	Drainage	0.620	0.3	0.603	0.27	0.594	0.3
	D4	stream	Drift	2.11	0.9	1.12	0.5	0.701	0.3
	D5	pond	Drainage	0.792	0.4	0.792	0.35	0.792	0.35
	D5	stream	Drift	2.26	**1.0**	1.19	0.5	0.579	0.26
	R1	pond	Drift / dry deposition	0.150	0.07	0.110	0.05	0.086	0.04
	R1	stream	Drift	1.68	0.7	0.90	0.4	0.435	0.2
	R3	stream	Runoff	15.9	**7.1**	15.9	**7.1**	15.9	**7.1**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 156: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation with of drift and runoff reduction for winter oilseed rape (1 × 750 g a.s./ha) – RAC = 2.25

BBCH	Vegetative strip			10 m		20 m	
	No spray buffer			10 m		20 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ETO-RAC	PEC_{sw} (µg/L)	PEC/ETO-RAC
00	D2	ditch	Drainage	43.9	**19.5**	43.9	**19.5**
	D2	stream	Drainage	29.7	**13.2**	29.7	**13.2**
	D3	ditch	Drift / dry deposition	0.761	0.3	0.401	0.2
	D4	pond	Drainage	0.326	0.1	0.311	0.1
	D4	stream	Drift	0.806	0.36	0.419	0.2
	D5	pond	Drainage	0.219	0.1	0.216	0.1
	D5	stream	Drift	0.865	0.4	0.450	0.2
	R1	pond	Drift / dry deposition	0.116	0.05	0.076	0.03
	R1	stream	Drift	0.632	0.3	0.330	0.15

	R3	stream	Runoff	3.5	**1.6**	1.83	0.8
20	D2	ditch	Drainage	77.7	**34.5**	77.7	**34.5**
	D2	stream	Drainage	48.5	**21.6**	48.5	**21.6**
	D3	ditch	Drift / dry deposition	0.802	0.36	0.429	0.2
	D4	pond	Drainage	0.617	0.27	0.596	0.26
	D4	stream	Drift	0.845	0.4	0.701	0.3
	D5	pond	Drainage	0.792	0.35	0.792	0.35
	D5	stream	Drift	0.902	0.4	0.575	0.26
	R1	pond	Drift / dry deposition	0.143	0.06	0.091	0.04
	R1	stream	Drift	0.679	0.3	0.357	0.16
	R3	stream	Runoff	7.23	**3.2**	3.79	**1.7**

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 157: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation of a no spray buffer for spring oilseed rape (1 × 1000 g a.s./ha) – Mesocosm RAC = 2.25

BBCH	**No spray buffer**			**5 m**	
	Scenario	**Water body**	**Dominant route of entry**	**PEC_{sw} (µg/L)**	**PEC/ETO-RAC**
00	D1	ditch	Drift	2.00	0.9
	D1	stream	Drift	2.06	0.9
	D3	ditch	Drift	1.72	0.8
	D4	pond	Drift / dry deposition	0.214	0.1
	D4	stream	Drift	1.80	0.8
	D5	pond	Drift / dry deposition	0.215	0.1
	D5	stream	Drift	1.85	0.8
	R1	pond	Runoff	0.244	0.1
	R1	stream	Runoff	1.70	0.8

Table 158: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation of nozzle reduction for spring oilseed rape (1 × 1000 g a.s./ha) – Mesocosm RAC = 2.25

BBCH	**Nozzle reduction**			**50%**		**75%**	
	Scenario	**Water body**	**Dominant route of entry**	**PEC_{sw} (µg/L)**	**PEC/ETO-RAC**	**PEC_{sw} (µg/L)**	**PEC/ETO-RAC**
00	D1	ditch	Drift	3.46	**1.5**	1.88	0.8
	D1	stream	Drift	2.75	**1.2**	1.48	0.7
	D3	ditch	Drift	3.17	**1.4**	1.58	0.7
	D4	pond	Drift / dry deposition	0.143	0.06	0.089	0.04
	D4	stream	Drift	2.46	**1.1**	1.24	0.6
	D5	pond	Drift / dry deposition	0.143	0.06	0.090	0.04
	D5	stream	Drift	2.53	**1.1**	1.28	0.6
	R1	pond	Runoff	0.186	0.08	0.143	0.06
	R1	stream	Runoff	2.13	0.95	1.70	0.8

Values in bold are above the trigger value of 1 and hence further consideration is needed for these scenarios

Table 159: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation with of drift and runoff reduction for spring oilseed rape (1 × 1000 g a.s./ha) – Mesocosm RAC = 2.25

BBCH	Vegetative strip			10 m	
	No spray buffer			10 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ETO-RAC
00	D1	ditch	Drift	1.20	0.5
	D1	stream	Drift	1.18	0.5
	D3	ditch	Drift	0.911	0.4
	D4	pond	Drift / dry deposition	0.155	0.07
	D4	stream	Drift	0.959	0.4
	D5	pond	Drift / dry deposition	0.156	0.07
	D5	stream	Drift	0.986	0.4
	R1	pond	Runoff	0.155	0.07
	R1	stream	Runoff	0.836	0.37

Table 160: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation of a no spray buffer for spring oilseed rape (1 × 750 g a.s./ha) – Mesocosm RAC = 2.25

BBCH	No spray buffer			5 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ETO-RAC
00	D1	ditch	Drift	1.49	0.66
	D1	stream	Drift	1.54	0.7
	D3	ditch	Drift	1.29	0.6
	D4	pond	Drift / dry deposition	0.161	0.07
	D4	stream	Drift	1.35	0.6
	D5	pond	Drift / dry deposition	0.161	0.07
	D5	stream	Drift	1.39	0.6
	R1	pond	Runoff	0.185	0.08
	R1	stream	Runoff	1.33	0.6

Table 161: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation of nozzle reduction for spring oilseed rape (1 × 750 g a.s./ha) – Mesocosm RAC = 2.25

BBCH	Nozzle reduction			50%		75%	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ETO-RAC	PEC_{sw} (µg/L)	PEC/ETO-RAC
00	D1	ditch	Drift	2.59	**1.15**	1.30	0.58
	D1	stream	Drift	2.06	0.9	1.03	0.46
	D3	ditch	Drift	2.38	**1.1**	1.19	0.53
	D4	pond	Drift / dry deposition	0.107	0.05	0.05	0.02
	D4	stream	Drift	1.84	0.8	0.92	0.41
	D5	pond	Drift / dry deposition	0.107	0.05	0.05	0.02
	D5	stream	Drift	1.90	0.8	0.95	0.42
	R1	pond	Runoff	0.142	0.06	0.07	0.03
	R1	stream	Runoff	1.60	0.7	0.80	0.36

Table 162: Higher tier risk assessment for macrophytes for dimethachlor based on FOCUS Step 4 with mitigation with of drift and runoff reduction for spring oilseed rape (1 × 750 g a.s./ha) – Mesocosm RAC = 2.25

BBCH	Vegetative strip			10 m	
	No spray buffer			10 m	
	Scenario	Water body	Dominant route of entry	PEC_{sw} (µg/L)	PEC/ETO-RAC
00	D1	ditch	Drift	0.896	0.40
	D1	stream	Drift	0.879	0.39
	D3	ditch	Drift	0.683	0.30
	D4	pond	Drift / dry deposition	0.117	0.05
	D4	stream	Drift	0.719	0.32
	D5	pond	Drift / dry deposition	0.117	0.05
	D5	stream	Drift	0.739	0.33
	R1	pond	Runoff	0.116	0.05
	R1	stream	Runoff	0.627	0.28

For the application of A5089H at 750 g a.s./ha and 1000 g a.s./ha at BBCH 00 and BBCH 20 to winter oilseed rape an acceptable risk at Tier I was demonstrated for all scenarios with the exception of D2 ditch, D2 stream and R3 stream. Other scenarios can be mitigated by either a 5 m no-spray buffer zone or by the use of 75% drift reducing nozzles. However, overall the mitigation measures required are driven by the algae risk assessment (see table 150).

For the application of A5089H at 1000 g a.s./ha at BBCH 00 spring oilseed rape an acceptable risk at Tier I was demonstrated for all scenarios with the exception of D1, D3, D4 and D5. The risk for these scenarios can be mitigated by using 75% drift reducing nozzles or by applying a 5 m no spray buffer zone.

It should be noted though that risk to aquatic organisms depends on (i) on the critical GAP use which may vary in the respective EU Member States, (ii) on MS specific PEC_{SW} modelling approaches and (iii) on nationally approved risk mitigation measures and restrictions of uses. Consequently, risk mitigation measures and use restrictions are identified and defined at Member State level. Furthermore it should be noted that the D2 scenario is only relevant for France and should also be handled on national level.

Dimethachlor metabolites

Table 163: Risk to aquatic organisms for dimethachlor metabolites for winter oilseed rape at 1000 g a.s./ha (FOCUS Step 1)

Crop/scenario	Test organism	Metabolite	Tier 1-RAC (µg/L)	Max PEC_{SW} (µg/L)	PEC/RAC
Winter oilseed rape, 1 x 1000 g a.s./ha, BBCH 00, BBCH 20	*Oncorhynchus mykiss*	CGA354742	>1 000	66.4	0.066
		CGA50266	>1 000	194	0.194
	Daphnia magna	CGA354742	>1 000	66.4	0.066
		CGA50266	>1 000	194	0.194
	Pseudokirchneriella subcapitata	CGA50266	>10 000	194	0.019
		CGA354742	>10 000	66.4	0.0066
		CGA373464	>4 300	68.9	0.016
		CGA369873	>10 000	54.6	0.0055
		SYN547047	7 900	28.5	0.0036

Crop/scenario	Test organism	Metabolite	Tier 1-RAC (µg/L)	Max PEC_{SW} (µg/L)	PEC/RAC
		CGA102935	1 960	29.4	0.015
		SYN530561	>10 000	10.4	0.0010
		CGA42443	8 200	46.3	0.006
	Lemna gibba	CGA354742	>10 200	66.4	0.0065
		CGA50266	>10 000	194	0.019
		CGA42443	8560	46.3	0.0054

Table 164: Risk to aquatic organisms for dimethachlor metabolites for winter oilseed rape at 750 g a.s./ha (FOCUS Step 1)

Crop/scenario	Test organism	Metabolite	Tier 1-RAC (µg/L)	Max PEC_{SW} (µg/L)	PEC/RAC
Winter oilseed rape, 1 x 750 g a.s./ha, BBCH 00, BBCH 20	*Oncorhynchus mykiss*	CGA354742	>1 000	49.8	0.050
		CGA50266	>1 000	145	0.145
	Daphnia magna	CGA354742	>1 000	49.8	0.050
		CGA50266	>1 000	145	0.145
	Pseudokirchneriella subcapitata	CGA50266	>10 000	145	0.0145
		CGA354742	>10 000	49.8	0.0049
		CGA373464	>4 300	51.7	0.012
		CGA369873	>10 000	41.0	0.0041
		SYN547047	7 900	21.3	0.0027
		CGA102935	1 960	22.0	0.011
		SYN530561	>10 000	7.78	0.0008
		CGA42443	8 200	34.7	0.0042
	Lemna gibba	CGA354742	>10 200	49.8	0.0049
		CGA50266	>10 000	145	0.0145
		CGA42443	8560	34.7	0.0041

Table 165: Risk to aquatic organisms for dimethachlor metabolites for spring oilseed rape (FOCUS Step 1)

Application rate (g a.s./ha)	Test organism	Metabolite	Tier 1-RAC (µg/L)	Max PEC_{SW} (µg/L)	PEC/RAC
1000 BBCH 00	*Oncorhynchus mykiss*	CGA354742	>1 000	66.4	0.066
		CGA50266	>1 000	194	0.194
	Daphnia magna	CGA354742	>1 000	66.4	0.066
		CGA50266	>1 000	155	0.194
	Pseudokirchneriella subcapitata	CGA50266	>10 000	194	0.0194
		CGA354742	>10 000	66.4	0.0066
		CGA373464	>4 300	68.9	0.016
		CGA369873	>10 000	54.6	0.0055
		SYN547047	7 900	28.5	0.0036
		CGA102935	1 960	29.4	0.015

Application rate (g a.s./ha)	Test organism	Metabolite	Tier 1-RAC (µg/L)	Max PEC_{SW} (µg/L)	PEC/RAC
		SYN530561	>10 000	10.4	0.0010
		CGA42443	8 200	46.3	0.0056
	Lemna gibba	CGA354742	>10 200	66.4	0.0065
		CGA50266	>10 000	194	0.0194
		CGA42443	8560	46.3	0.0054
750 BBCH 00	*Oncorhynchus mykiss*	CGA354742	>1 000	49.8	0.050
		CGA50266	>1 000	145	0.145
	Daphnia magna	CGA354742	>1 000	49.8	0.050
		CGA50266	>1 000	145	0.145
	Pseudokirchneriella subcapitata *Pseudokirchneriella subcapitata*	CGA354742	>10 000	49.8	0.0049
		CGA373464	>4 300	51.7	0.012
		CGA369873	>10 000	41.0	0.0041
		SYN547047	7 900	21.3	0.0027
		CGA50266	>10 000	145	0.0145
		CGA102935	1 960	22.0	0.011
		SYN530561	>10 000	7.78	0.00078
		CGA42443	5 380	34.7	0.0064
	Lemna gibba	CGA354742	>10 200	49.8	0.0049
		CGA50266	>10 000	145	0.0145
		CGA42443	8560	34.7	0.0041

All of the PEC/RAC values are below the trigger of 1 indicating acceptable risk to aquatic organisms for metabolites of dimethachlor following application of A5089H according to the proposed use pattern at FOCUS Step 1 with no requirement for risk mitigation.

Bees

For the purposes of this risk assessment, the evaluation of the risk for honeybees was performed in accordance with the principles of the "EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees)" (EFSA Journal 2014; 11(7):3295).

Screening step

Table 166: Screening step of the risk for bees due to the use of A5089H in oilseed rape – dimethachlor (1000g/ha)

Intended use **Active substance**	DW Dimethachlor				
Application rate (g a.s./ha)	1000				
Test design	**Endpoint (lab.) (µg a.s./bee)**	**Single application rate**	**Shortcut Value**	**HQ/ ETR**	**Trigger**

Acute contact toxicity LD_{50}	100	1000 g a.s./ha	1	10	42
Acute oral toxicity LD_{50}	104.9	1000 g a.s./ha	7.6	0.07	0.2
Chronic adult oral toxicity LDD_{50}	48.2	1000 g a.s./ha	7.6	**0.158**	0.03
Larval development oral toxicity NOED	91.6	1000 g a.s./ha	4.4	0.05	0.2

HQ (hazard quotients) and ETR (exposure toxicity ratio) for oral and contact exposure. HQ/ETR values shown in bold breach the relevant trigger.

Table 167: Screening step assessment of the risk for bees due to the use of A5089H in oilseed rape – dimethachlor (750g/ha)

Intended use **Active substance**	DW Dimethachlor				
Application rate (g a.s./ha)	750				
Test design	**Endpoint (lab.) (µg a.s./bee)**	**Single application rate**	**Shortcut Value**	**HQ/ ETR**	**Trigger**
Acute contact toxicity LD_{50}	100	750 g a.s./ha	1	7.5	42
Acute oral toxicity LD_{50}	104.9	750 g a.s./ha	7.6	0.05	0.2
Chronic adult oral toxicity LDD_{50}	48.2	750 g a.s./ha	7.6	**0.118**	0.03
Larval development oral toxicity NOED	91.6	750 g a.s./ha	4.4	0.04	0.2

HQ (hazard quotients) and ETR (exposure toxicity ratio) for oral and contact exposure. HQ/ETR values shown in bold breach the relevant trigger.

The screening step indicated no risk from acute contact or oral exposure to adult honey bees or chronic oral risk to honey bee larvae, following use of A5089H. However, a potential chronic oral risk for honey bee adults was demonstrated. Therefore, a Tier 1 chronic assessment for the treated crop, field margin, adjacent crop and next crop are provided below.

Tier 1 - Chronic Adult Oral Risk Assessment

The screening step risk assessment indicated a potential chronic risk to adult bees and therefore a Tier 1 assessment for the treated crop is provided for oilseed rape. HQ/ ETR values which are below the trigger values indicate an acceptable risk to bees.
Applications to oilseed rape are made pre-flowering and therefore exposure of bees via pollen and nectar from the treated crop cannot be excluded for the risk assessment. In addition, an off-field risk assessment is also shown below for field margin and adjacent crop, respectively. Exposure to treated weeds is not considered a relevant exposure scenario according to the guidance as evidence is available to demonstrate that in arable crops flowering

attractive weeds are not present at >10% of the area of use: Maynard *et al.* (2015)[31].

Table 168: Tier I assessment of the chronic risk for bees due to the use of A5089H in oilseed rape for the treated crop (pre-emergence)

Intended use		DW					
Active substance		Dimethachlor					
Application rate (g/ha)		1000					
Test design	**Endpoint (lab.)**	**Single application rate**	**Shortcut Value (downward spray)**	**TWA**	**fDep/ Ef**	**HQ/ ETR**	**Trigger**
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	1000 g/ha	0.54	0.72	1	0.008	0.03
Application rate (g/ha)		750					
Test design	Endpoint (lab.)	Single application rate	Shortcut Value (downward spray)	TWA	fDep/ Ef	HQ/ ETR	Trigger
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	750 g/ha	0.54	0.72	1	0.006	0.03

HQ (hazard quotients) and ETR (exposure toxicity ratio) for oral and contact exposure. HQ/ETR values shown in **bold** breach the relevant trigger.

Table 169: Tier I assessment of the chronic risk for bees due to the use of A5089H in oilseed rape for the treated crop (post-emergence)

Intended use		DW					
Active substance		Dimethachlor					
Application rate (g/ha)		1000					
Test design	**Endpoint (lab.)**	**Single application rate**	**Shortcut Value (downward spray)**	**TWA**	**fDep/ Ef**	**HQ/ ETR**	**Trigger**
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	1000 g/ha	5.8	0.72	1	**0.087**	0.03
Application rate (g/ha)		750					

[31] Exposure to treated weeds is not considered a relevant exposure scenario according to the guidance as evidence is available to demonstrate that in arable crops flowering attractive weeds are not present at >10% of the area of use: Maynard *et al.* (2015), Weeds in the treated field - a realistic scenario for pollinator risk assessment? Proceedings of 12th International Symposium of the ICP-PR Bee Protection Group, Ghent (Belgium), September 15-17, 2014. Available at: https://ojs.openagrar.de/index.php/JKA/article/view/5318

Test design	Endpoint (lab.)	Single application rate	Shortcut Value (downward spray)	TWA	fDep/ Ef	HQ/ ETR	Trigger
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	750 g/ha	5.8	0.72	1	**0.065**	0.03

HQ (hazard quotients) and ETR (exposure toxicity ratio) for oral and contact exposure. HQ/ETR values shown in **bold** breach the relevant trigger.

Table 170: Tier I assessment of the chronic risk for bees due to the use of A5089H in oilseed rape for field margin (pre-emergence and post-emergence)

Intended use		DW					
Active substance		Dimethachlor					
Application rate (g/ha)		1000					
Test design	**Endpoint (lab.)**	**Single application rate**	**Shortcut Value (upward spray)**	**TWA**	**fDep/ Ef**	**HQ/ ETR**	**Trigger**
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	1000 g/ha	2.9	0.72	0.0092	0.000	0.03
Application rate (g/ha)		750					
Test design	Endpoint (lab.)	Single application rate	Shortcut Value (upward spray)	TWA	fDep/ Ef	HQ/ ETR	Trigger
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	1000 g/ha	2.9	0.72	0.0092	0.000	0.03

HQ (hazard quotients) and ETR (exposure toxicity ratio) for oral and contact exposure. HQ/ETR values shown in bold breach the relevant trigger.

Table 171: Tier I assessment of the chronic risk for bees due to the use of A5089H in oilseed rape for adjacent crop (pre-emergence and post-emergence)

Intended use		DW					
Active substance		Dimethachlor					
Application rate (g/ha)		1000					
Test design	**Endpoint (lab.)**	**Single application rate**	**Shortcut Value (upward spray)**	**TWA**	**fDep/ Ef**	**HQ/ ETR**	**Trigger**
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	1000 g/ha	5.8	0.72	0.0033	0.000	0.03
Application rate (g/ha)		750					

Test design	Endpoint (lab.)	Single application rate	Shortcut Value (upward spray)	TWA	fDep/ Ef	HQ/ ETR	Trigger
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	750 g/ha	5.8	0.72	0.0033	0.000	0.03

HQ (hazard quotients) and ETR (exposure toxicity ratio) for oral and contact exposure. HQ/ETR values shown in bold breach the relevant trigger.

Table 172: Tier I assessment of the chronic risk for bees due to the use of A5089H in oilseed rape for next crop (pre-emergence and post-emergence)

Intended use		DW					
Active substance		Dimethachlor					
Application rate (g/ha)		1000					
Test design	**Endpoint (lab.)**	**Single application rate**	**Shortcut Value (upward spray)**	**TWA**	**fDep/ Ef**	**HQ/ ETR**	**Trigger**
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	1000 g/ha	0.54	0.72	1	0.008	0.03
Application rate (g/ha)		750					
Test design	Endpoint (lab.)	Single application rate	Shortcut Value (upward spray)	TWA	fDep/ Ef	HQ/ ETR	Trigger
Chronic adult oral toxicity LDD_{50}	48.2 µg a.s./bee/day	750 g/ha	0.54	0.72	1	0.006	0.03

HQ (hazard quotients) and ETR (exposure toxicity ratio) for oral and contact exposure. HQ/ETR values shown in bold breach the relevant trigger.

The Tier 1 chronic assessment for field margins, adjacent crop and next crop were appropriate and indicate acceptable risk from oral exposure of adult honey bees following applications of A5089H to oilseed rape.
However, a potential chronic oral risk to adult honey bees was highlighted for the treated crop scenario. To address this potential risk, a pollen and nectar residue study was conducted in oilseed rape following the intended use rate for A5089H.

Higher tier assessment - Chronic Adult Oral Risk Assessment Treated Crop

In order to refine the potential chronic risk to adult bees from exposure to dimethachlor in pollen and nectar following applications of A5089H, a residue study in pollen and nectar was conducted (Appeltauer 2019; A5089H_10426). For further details please see Volume 3 – B.9 (CA). Oilseed rape was treated once with A5089H at a use rate of 2 L product/ha (1 kg dimethachlor/ha). Concentrations of dimethachlor and metabolite SYN550004 were measured in pollen and nectar samples using LC-MS/MS. All measured concentrations of dimethachlor and SYN550004 were <LOQ (0.01 mg/kg). Therefore, the exposure to A5089H to adult bees foraging in the treated crop during oilseed rape flowering is expected to be very low and consequently risk is considered to be acceptable.

Metabolites

In accordance with Regulation (EU) 283/2013, a consideration of the risk to bees from metabolites is needed. It is suggested that the methodology in the EFSA (2013) Bee guidance[32] is followed to identify which plant metabolites should be assessed. As a starting point the information from plant metabolism studies are summarised in Table 173 (see Volume 3 – B.7 (CA)) and can be used as a surrogate for pollen and nectar.

Table 173: Metabolites found in foliage and seed of oilseed rape after application with [14C]-Dimethachlor (1000 g/ha).

Component	**Residue Levels**			
	Foliage		**Seed**	
	%TRR	**mg/kg**	**%TRR**	**mg/kg**
CGA50266	20.8	0.033	7.9	0.004
CGA39981	6.4	0.012	0.9	<0.001
CGA354742	6.8	0.471	4.5	0.009
CGA103699	4.1	0.282	N/D	N/D
SYN547047	6.5	0.450	5.3	0.010
SYN550004	46.8	3.261	N/D	N/D
U2[a]	6.9	0.482	N/D	N/D
U3[a]	5.5	0.381	<LOD	<LOD
U4[a]	8.1	0.564	N/D	N/D
U5[a]	3.7	0.259	<LOD	<LOD
Oleic acid	N/D	N/D	N/Q	N/Q

[a] Structures of U2, U3, U4 and U5 were proposed based on the mass spectra and chromatographic behaviour. The exact position of the hydroxyl group in the ring of U2 and U3 could not be determined by mass spectrometry.
N/D: Not detected
N/Q: Not quantified

According to the risk assessment scheme for metabolites in the EFSA (2013) Bee GD[25], identified metabolites formed in amounts of >10% or 0.01 mg/kg require further consideration. Further assessment is required for metabolites containing the toxophore relevant for bee toxicity. No further assessment is required for metabolites that has lost the toxic moiety. For dimethachlor there are two radio-labelled plant metabolism studies available in oilseed rape (see Volume 3 – B.7 (CA)).

[32] European Food Safety Authority, 2013. EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees). EFSA Journal 2013;11(7):3295, 268 pp., doi:10.2903/j.efsa.2013.3295

All metabolites were found at levels >0.01 mg/kg and should therefore be further addressed in the risk assessment. SYN550004 was the principle metabolite identified in foliage (46.8% TRR; 3.261 mg/kg). A pollen and nectar residue study (see Volume 3 – B.9 (CA); Appeltauer 2019; A5089H_10426) showed that the concentration of SYN550004 was <LOQ in all pollen and nectar samples taken at intervals during flowering. Therefore, it is concluded that the potential exposure of foraging bees to SYN550004 is negligible and a potential risk is acceptable.

From the remaining metabolites, CGA50266 was found at the highest concentrations (20.8 %TRR; 0.033 mg/kg). Therefore the potential risk to bees from this metabolite was assessed by assuming a 10-fold toxicity compared to dimethachlor in the absence of data, and acute and chronic ETR values calculated accordingly. As dimethachlor metabolite CGA50266 is present at the highest concentrations after SYN550004 it is considered that this covers the risk from the remaining metabolites. The corresponding assessment is provided below.

Metabolites - Acute Contact Adult

The contact risk is not relevant where residues of concern are those potentially expressed in pollen and nectar, where the relevant route of exposure is via consumption, but the risk assessment is included here for completeness (Table 9.9-72).

The HQ is calculated for each metabolite and compared with the EFSA trigger of 42. The endpoint from the acute adult contact toxicity study with parent has been assessed at the screening step using a safety factor of 10 on the endpoint. Exposure is adjusted according to the molecular weight and % TRR of each metabolite according to EFSA Bee Guidance (2014) and the EFSA Bee Tool.

$$HQ = \frac{\text{Application rate} * (\text{molecular weight of metabolite} / \text{molecular weight of parent}) * \%\text{TRR}}{LD50/10}$$

Table 174: Screening assessment of the acute contact risk to adult honeybee due to the use of formulation A5089H in the treated crop for oilseed rape - metabolites

Metabolite	Fraction of metabolite formed (max. percentage of TRR observed in any matrix analysed)	Molecular weight (g/mol)	Oilseed rape (750 g a.s./ha) screening HQ	Oilseed rape (1000 g a.s./ha) screening HQ
Dimethachlor (parent)	N/A	255.8	-	-
CGA50266	20.8	251.3	15.3	20.4
SYN550004	46.8	255.8[1]	33.5	**44.6**

N/A: not applicable

HQ (hazard quotients) values shown in **bold** breach the relevant trigger.

[1] Molar weight is not known. Therefore, the same molar weight as the parent was assumed.

The HQ values are above the EFSA trigger of 42 indicating an unacceptable acute contact risk to adult honeybees following use of A5089H on oilseed rape.

A pollen and nectar residue study (see Volume 3 – B.9 (CA); Appeltauer 2019; A5089H_10426) showed that the concentration of SYN550004 was <LOQ in all pollen and nectar samples taken at intervals during flowering. Therefore, it is concluded that the potential exposure of foraging bees to SYN550004 is negligible and a potential risk is acceptable.

Metabolites - Acute Oral Adult

The ETR is calculated for each metabolite and compared with the EFSA trigger of 0.2 (Table 175). The endpoint from the acute adult oral toxicity study with parent has been assessed at the screening step using a safety factor of 10 on the endpoint. Exposure is adjusted according to the molecular weight and % TRR of each metabolite according to EFSA Bee Guidance (2014) and the EFSA Bee Tool.

$$ETR = \frac{Application\ rate * DT_{50} * \left(\frac{MW_{et}}{MW_{parent}}\right) * \%OM}{LD_{50}/10}$$

Table 175: Screening assessment of the acute oral risk to adult honeybee due to the use of formulation A5089H in the treated crop for oilseed rape - metabolites

Metabolite	Fraction of metabolite formed (max. percentage of TRR observed in any matrix analysed)	Molecular weight (g/mol)	Oilseed rape (750 g a.s./ha) screening $ETR_{acute\ adult\ oral}$	Oilseed rape (1000 g a.s./ha) screening $ETR_{acute\ adult\ oral}$
Dimethachlor (parent)	N/A	255.8		-
CGA50266	20.8	251.3	0.11	0.15
SYN550004	46.8	255.8	0.00	0.04

N/A: not applicable
HQ (hazard quotients) values shown in **bold** breach the relevant trigger.

The ETR values are below the EFSA trigger of 0.2 indicating an acceptable acute oral risk to adult honeybees following use of A5089H in oilseed rape.

Metabolites - Chronic Oral Adult

The ETR calculation in Approach 2 for parent is adjusted for metabolites by taking into account the molecular weight and percentage composition of the metabolite as shown in the EFSA Bee GD. The LD_{50} is divided by 10 but the LDD_0 is also divided by 10 as the slope of the dose response for the metabolite is equivalent to that of the parent.

$$\text{Calculation for metabolite ETR} = \frac{(\text{µg/bee/day for parent} * (mwmet/mwparent) * \%\,TRR) - \left(\frac{LDD0}{10}\right)}{(LDD50/10) - (LDD0/10)}$$

Table 176: Tier 1 assessment of the chronic risk to adult honeybee due to the use of formulation A5089H in the treated crop for oilseed rape - metabolites

Metabolite	Fraction of metabolite formed (max. percentage of TRR observed in any matrix analysed)	Molecular weight (g/mol)	Oilseed rape treated crop (750 g a.s./ha) Tier 1 $ETR_{chronic\ adult\ oral}$	Oilseed rape treated crop (1000 g a.s./ha) Tier 1 $ETR_{chronic\ adult\ oral}$
Dimthachlor (parent)	N/A	255.8	-	-
CGA50266	20.8	251.3	-1.986	-2.007
SYN550004	46.8	255.8	-1.873	-1.922

N/A: not applicable
ETR values in **bold** indicate a potential risk

The ETR values are below the EFSA trigger of 0.03 indicating an acceptable chronic oral risk to adult honeybees following use of A5089H in oilseed rape.

Metabolites - Chronic Larval

The TER calculation for parent is adjusted for metabolites by taking into account the molecular weight and percentage composition of the metabolite as shown in the EFSA Bee GD.

$$ETR = \frac{(NOEC/10)}{\text{mg/kgfor parent} * (mwmet/mwparent) * \%\,TRR)}$$

Table 177: Tier 1 assessment of the chronic risk to honey bee larvae due to the use of formulation A5089H in the treated crop for oilseed rape - metabolites

etabolite	Fraction of metabolite formed (max. percentage of TRR observed in any matrix analysed)	Molecular weight (g/mol)	Oilseed rape treated crop (750 g a.s./ha) Tier 1 $ETR_{chronic\ larval\ oral}$	Oilseed rape treated crop (1000 g a.s./ha) Tier 1 $ETR_{chronic\ larval\ oral}$
Dimethachlor (parent)	N/A	255.8	-	-
CGA50266	8.1	255.8	620	465
SYN550004	46.8	255.8	271	203

N/A: not applicable
ETR values in **bold** indicate a potential risk

The chronic ETR values are greater than the trigger value of 1 indicating that the chronic risk to honey bee larvae is acceptable following use of A5089H according to the proposed uses.

Non-target arthropods other than bees

The risk to non-target arthropods is assessed using the approach recommended in the published ESCORT 2 document (**Candolfi *et al.* 2001**)[33] and the **EC Guidance Document on Terrestrial Ecotoxicology**[34].

Risk assessment for other non-target arthropods - in-field

Tier I risk assessment

Tier I risk assessment is based on hazard quotient approach. The hazard quotient (HQ) is derived from predicted environmental residue (PER) and LR_{50} values generated for *Aphidius rhopalosiphi* and *Typhlodromus pyri* on glass plates (worst case exposure). Bold values indicate the risk to non-target arthropods.

Table 178: Tier 1 in-field risk assessment for non-target arthropods

Crop	Application rate (mL A5089H/ha)	Species	Test type	LR_{50} (mL product/ha)	In-field PER (mL/ha)	Value	Trigger
Oilseed rape	2000	*Aphidius rhopalosiphi*	Tier I	181.4	2000	**11**	2
		Typhlodromus pyri		1305		1.53	2
	1500	*Aphidius rhopalosiphi*	Tier I	181.4	1500	**8.27**	2
		Typhlodromus pyri		1305		1.15	2

[33] Candolfi MP, Barrett KL, Campbell PJ, Forster R, Grandy N, Huet M-C, Lewis G, Oomen PA, Schmuck R, Vogt H (2000) 'Guidance Document on regulatory testing procedures for plant protection products with non-target arthropods' From the workshop, European Standard Characteristics of Non-target Arthropod Regulatory Testing (ESCORT 2) 21-23 March 2000.
[34] EC Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC, SANCO/10329, 17 October 2002.

Higher tier risk assessment

Higher tier tests with the two 'indicator' species (*Aphidius rhopalosphi* and *Typhlodromus pyri*) have been conducted according to the principles of ESCORT 2 and summarised in the table below. According to ESCORT 2, in higher tier tests, lethal and sublethal effects <50% compared to the control, at test rates equivalent to the relevant PER are considered acceptable.

Studies have also been conducted with *Chrysoperla carnea* and *Pardosa* spp. in which the arthropods were exposed to the test substance on inert substrates (glass plates for *C. carnea* and quartz sand for *Pardosa* spp.). These species are not considered in the Tier 1 risk assessment according to ESCORT II and hence are considered to be higher tier tests and are suitable for use in the risk assessment presented below.

Table 179: In-field risk assessment for non-target arthropods

Crop	Application rate (mL A5089H/ha)	Species	Test type	Endpoint	Value (mL/ha)	In-field foliar/soil PER (mL/ha)	Acceptable risk?
Oilseed rape	2000	*Aphidius rhopalosiphi*	Tier II	LR_{50}	>6400	2000	Yes
				Sublethal effects <50%	>6400		
		Typhlodromus pyri		LR_{50}	>3000		Yes
				Sublethal effects <50%	>3000		
		Chrysoperla carnea [a]		LR_{50}	>3000		Yes
		Pardosa spp.		LR_{50}	>3000		Yes
				Sublethal effects <50%	>3000		
	1500	*Aphidius rhopalosiphi*	Tier II	LR_{50}	>6400	1500	Yes
				Sublethal effects <50%	>6400		
		Typhlodromus pyri		LR_{50}	>3000		Yes
				Sublethal effects <50%	>3000		
		Chrysoperla carnea a		LR_{50}	>3000		Yes
		Pardosa spp.		LR_{50}	>3000		Yes
				Sublethal effects <50%	>3000		

[a] Although fecundity effects were evaluated in this test the results are only considered to be qualitative and the thresholds of ≥ 15 eggs/female/day and the mean egg viability of ≥ 70% are currently viewed as being indicative of no harmful treatment effects (Vogt *et al*., 2000). Hence a quantitative ER_{50} is not derived in this test

The in-field PER values were lower than the LR_{50} and sublethal endpoints for all species. This indicates that the in-field risk to non-target arthropods is acceptable following application of A5089H according to the proposed use patterns.

Risk assessment for other non-target arthropods - off-field

The in-field HQ values for *Aphidius rhopalosiphi* are higher than trigger value 2 for both application rates indicating the in-field risk to non-target arthropods. The in-field HQ values for *Typhlodromus pyri* are lower than trigger value 2 for both application rates indicating the in-field risk to non-target arthropods is acceptable following application of A5089H according to the proposed use patterns.

Table 180: Tier I off-field risk assessment values for non-target arthropods

Crop	Application rate (mL A5089H/ha)	Species	Test type	LR_{50} (mL product/ha)	Off-field PER (mL/ha)	Value	Trigger
Oilseed rape	2000	*Aphidius rhopalosiphi*	Tier I	181.4	5.54	0.03	2
		Typhlodromus pyri		1305		0.004	2
	1500	*Aphidius rhopalosiphi*	Tier I	181.4	4.16	0.023	2
		Typhlodromus pyri		1305		0.003	2

The off-field PER values were lower than the trigger values of 2 for both species. This indicates that the off-field risk to non-target arthropods is acceptable following application of A5089H according to the proposed use patterns.

Earthworms

The risk assessment for soil meso- and macro-fauna followed the approaches recommended in the EC Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002). For details of the risk assessment please refer to the Volume 3 – B.9 (CP).

Table 181: First-tier assessment of the chronic risk for earthworms due to the use of A5089H in oilseed rape (1 x 1000 g a.s/ha – BBCH 00)

Test substance	Log Pow value	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	2.17[a]	$NOEC_{corr}$ = 61.5	2.81[c]	22
Dimethachlor	2.17[a]	$NOEC_{corr}$ = 29[e]	1.33[c]	44
CGA354742	-2.1[a]	EC_{10} = 158.2	0.325[d]	487
SYN547047	-2.8[a]	NOEC = 1000	0.117[d]	8547
CGA50266	1.43[b]	NOEC = 1000	0.469[d]	2132
CGA102935	-4.1[a]	NOEC = 1000	0.118[c]	8475
CGA42443	1.87[b]	NOEC = 16.35	0.073[d]	224

[a] Experimental log Pow value
[b] Calculated log Pow value
[c] Initial PECs
[d] Peak accumulation PECs

Table 182: First-tier assessment of the chronic risk for earthworms due to the use of A5089H in oilseed rape (1 x 1000 g a.s/ha – BBCH 20)

Test substance	Log Pow value	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	2.17[a]	$NOEC_{corr}$ = 61.5	0.562[c]	117
Dimethachlor	2.17[a]	$NOEC_{corr}$ = 29[e]	0.267[c]	108
CGA354742	-2.1[a]	EC_{10} = 158.2	0.065[d]	2434

SYN547047	-2.8[a]	NOEC = 1000	0.023[d]	43478
CGA50266	1.43[b]	NOEC = 1000	0.094[d]	10638
CGA102935	-4.1[a]	NOEC = 1000	0.024[c]	41667
CGA42443	1.87[b]	NOEC = 16.35	0.015[d]	1090

[a] Experimental log Pow value
[b] Calculated log Pow value
[c] Initial PECs
[d] Peak accumulation PECS

Table 183: First-tier assessment of the chronic risk for earthworms due to the use of A5089H in oilseed rape (1 x 750 g a.s/ha – BBCH 00)

Test substance	**Log Pow value**	**Endpoint (mg/kg dw)**	**PEC_{soil} (mg/kg dw)**	**TER_{lt} (criterion TER ≥ 5)**
A5089H	2.17[a]	$NOEC_{corr}$ = 61.5	2.11[c]	29
Dimethachlor	2.17[a]	$NOEC_{corr}$ = 29[e]	1.00[c]	29
CGA354742	-2.1[a]	EC_{10} = 158.2	0.244[d]	648
SYN547047	-2.8[a]	NOEC = 1000	0.088[d]	13164
CGA50266	1.43[b]	NOEC = 1000	0.352[d]	2841
CGA102935	-4.1[a]	NOEC = 1000	0.088[c]	11364
CGA42443	1.87[b]	NOEC = 16.35	0.055[d]	297

[a] Experimental log Pow value
[b] Calculated log Pow value
[c] Initial PECs
[d] Peak accumulation PECS

Table 184: First-tier assessment of the chronic risk for earthworms due to the use of A5089H in oilseed rape (1 x 750 g a.s/ha – BBCH 20)

Test substance	**Log Pow value**	**Endpoint (mg/kg dw)**	**PEC_{soil} (mg/kg dw)**	**TER_{lt} (criterion TER ≥ 5)**
A5089H	2.17[a]	$NOEC_{corr}$ = 61.5	0.421[c]	146
Dimethachlor	2.17[a]	$NOEC_{corr}$ = 29[e]	0.200[c]	145
CGA354742	-2.1[a]	EC_{10} = 158.2	0.049[d]	3229
SYN547047	-2.8[a]	NOEC = 1000	0.017[d]	58823
CGA50266	1.43[b]	NOEC = 1000	0.071[d]	14084
CGA102935	-4.1[a]	NOEC = 1000	0.018[c]	55555
CGA42443	1.87[b]	NOEC = 16.35	0.011[d]	1486

[a] Experimental log Pow value
[b] Calculated log Pow value
[c] Initial PECs
[d] Peak accumulation PECS

The long-term TER values all exceed the Commission Regulation (EU) No. 546/2011 long-term trigger value of 5, indicating that the long-term risk to earthworms is acceptable following use of A5089H according to the proposed use pattern.

Non-target soil meso- and macrofauna (other than earthworms)

The risk assessment for soil meso- and macro-fauna followed the approaches recommended in the EC Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002). For details of the risk assessment please refer to Volume 3 - B.9 (CP).

Table 185: First-tier assessment of the chronic risk for *Folsomia candida* due to the use of A5089H in oilseed rape at 1 x 1000 g a.s./ha – BBCH 00

Test substance	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	$NOEC_{corr}$ = 18.5	2.81[a]	6.58
Dimethachlor	$NOEC_{corr}$ = 8.73	1.33[a]	6.56
CGA354742	NOEC = 1000	0.325[d]	3077
SYN547047	NOEC = 1000	0.117[d]	8547
CGA50266	NOEC = 555.6	0.469[d]	1185
CGA102935	EC_{10} = 27.167	0.118[c]	230
CGA42443	EC_{10} = 24.28	0.073[d]	333

[a] Initial PECs
[b] Peak accumulation PECs

Table 186: First-tier assessment of the chronic risk for *Folsomia candida* due to the use of A5089H in oilseed rape at 1 x 1000 g a.s./ha – BBCH 20

Test substance	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	$NOEC_{corr}$ = 18.5	0.562[a]	35
Dimethachlor	$NOEC_{corr}$ = 8.73	0.267[a]	33
CGA354742	NOEC = 1000	0.065[d]	15385
SYN547047	NOEC = 1000	0.023[d]	43478
CGA50266	NOEC = 555.6	0.094[d]	5911
CGA102935	EC_{10} = 27.167	0.024[c]	1132
CGA42443	EC_{10} = 24.28	0.015[d]	1619

[a] Initial PECs
[b] Peak accumulation PECs

Table 187: First-tier assessment of the chronic risk for *Folsomia candida* due to the use of A5089H in oilseed rape at 1 x 750 g a.s./ha – BBCH 00

Test substance	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	$NOEC_{corr}$ = 18.5	2.11[a]	9
Dimethachlor	$NOEC_{corr}$ = 8.73	1.00[a]	9
CGA354742	NOEC = 1000	0.244[d]	4098
SYN547047	NOEC = 1000	0.088[d]	11364
CGA50266	NOEC = 555.6	0.352[d]	1578
CGA102935	EC_{10} = 27.167	0.088[c]	309
CGA42443	EC_{10} = 24.28	0.055[d]	441

[a] Initial PECs
[b] Peak accumulation PEC_S

Table 188: First-tier assessment of the chronic risk for *Folsomia candida* due to the use of A5089H in oilseed rape at 1 x 750 g a.s./ha – BBCH 20

Test substance	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	$NOEC_{corr}$ = 18.5	0.421[a]	44
Dimethachlor	$NOEC_{corr}$ = 8.73	0.200[a]	44
CGA354742	NOEC = 1000	0.049[d]	20408
SYN547047	NOEC = 1000	0.017[d]	58824
CGA50266	NOEC = 555.6	0.071[d]	7825
CGA102935	EC_{10} = 27.167	0.018[c]	1509
CGA42443	EC_{10} = 24.28	0.011[d]	2207

[a] Initial PECs
[b] Peak accumulation PEC_S

Table 189: First-tier assessment of the chronic risk for *Hypoaspis aculiefer* due to the use of A5089H in oilseed rape at 1 x 1000 g a.s./ha – BBCH 00

Test substance	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	EC_{10corr} = 137	2.81[a]	49
Dimethachlor	EC_{10corr} = 64.8	1.33[a]	49
CGA354742	EC_{10} = 67	0.325[d]	206
SYN547047	EC_{10} = 16.2	0.117[d]	138
CGA50266	NOEC = 16.35	0.469[d]	35
CGA102935	NOEC = 29.42	0.118[c]	249
CGA42443	NOEC = 555.6	0.073[d]	7611

[a] Initial PECs
[b] Peak accumulation PECs

Table 190: First-tier assessment of the chronic risk for *Hypoaspis aculiefer* due to the use of A5089H in oilseed rape at 1 x 1000 g a.s./ha – BBCH 20

Test substance	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	EC_{10corr} = 137	0.562[a]	261
Dimethachlor	EC_{10corr} = 64.8	0.267[a]	243
CGA354742	EC_{10} = 67	0.065[d]	1031
SYN547047	EC_{10} = 16.2	0.023[d]	704
CGA50266	NOEC = 16.35	0.094[d]	174
CGA102935	NOEC = 29.42	0.024[c]	1226
CGA42443	NOEC = 555.6	0.015[d]	37040

[a] Initial PECs
[b] Peak accumulation PECs

Table 191: First-tier assessment of the chronic risk for *Hypoaspis aculiefer* due to the use of A5089H in oilseed rape at 1 x 750 g a.s./ha – BBCH 00

Test substance	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	EC_{10corr} = 137	2.11[a]	65
Dimethachlor	EC_{10corr} = 64.8	1.00[a]	65
CGA354742	EC_{10} = 67	0.244[d]	275
SYN547047	EC_{10} = 16.2	0.088[d]	184
CGA50266	NOEC = 16.35	0.352[d]	46
CGA102935	NOEC = 29.42	0.088[c]	334
CGA42443	NOEC = 555.6	0.055[d]	10102

[a] Initial PECs
[b] Peak accumulation PECs

Table 192: First-tier assessment of the chronic risk for *Hypoaspis aculiefer* due to the use of A5089H in oilseed rape at 1 x 750 g a.s./ha – BBCH 20

Test substance	Endpoint (mg/kg dw)	PEC_{soil} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
A5089H	EC_{10corr} = 137	0.421[a]	326
Dimethachlor	EC_{10corr} = 64.8	0.200[a]	324
CGA354742	EC_{10} = 67	0.049[d]	1367
SYN547047	EC_{10} = 16.2	0.017[d]	953
CGA50266	NOEC = 16.35	0.071[d]	230
CGA102935	NOEC = 29.42	0.018[c]	1634
CGA42443	NOEC = 555.6	0.011[d]	50509

[a] Initial PECs
[b] Peak accumulation PECs

The long-term TER values exceed the Commission Regulation (EU) No. 546/2011 long-term trigger value of 5, indicating that the long-term risk to soil arthropods is acceptable following use of A5089H according to the proposed use pattern.

The risk assessment for soil nitrogen transformation followed the approaches recommended in the EC Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002). For details of the risk assessment please refer to Volume 3 – B.9 (CP).

Soil microorganisms

Table 193: Assessment of the risk for effects on soil micro-organisms due to the use of A5089H in oilseed rape at 1 x 1000 g a.s./ha – BBCH 00

Test substance	NOEC (mg/kg dw)	PEC_{soil} (mg/kg dw)	Ratio of NOEC:PECs
A5089F	NOEC = 21.08	2.81[a]	7.5
Dimethachlor	NOEC = 10	1.33[a]	7.5
CGA354742	NOEC = 2.02	0.325[d]	6.2
SYN547047	NOEC = 5	0.117[d]	42.7
CGA50266	NOEC = 3.79	0.469[d]	8.1
CGA102935	NOEC = 5	0.118[c]	42.4
CGA42443	NOEC = 5	0.073[d]	68.5

[a] Initial PECs
[b] Peak accumulation PECs

Table 194: Assessment of the risk for effects on soil micro-organisms due to the use of A5089H in oilseed rape at 1 x 1000 g a.s./ha – BBCH 20

Test substance	NOEC (mg/kg dw)	PEC_{soil} (mg/kg dw)	Ratio of NOEC:PECs
A5089F	NOEC = 21.08	0.562[a]	40
Dimethachlor	NOEC = 10	0.267[a]	37
CGA354742	NOEC = 2.02	0.065[d]	31
SYN547047	NOEC = 5	0.023[d]	217
CGA50266	NOEC = 3.79	0.094[d]	40
CGA102935	NOEC = 5	0.024[c]	208
CGA42443	NOEC = 5	0.015[d]	333

[a] Initial PECs
[b] Peak accumulation PECs

Table 195: Assessment of the risk for effects on soil micro-organisms due to the use of A5089H in oilseed rape at 1 x 750 g a.s./ha – BBCH 00

Test substance	NOEC (mg/kg dw)	PEC_{soil} (mg/kg dw)	Ratio of NOEC:PECs
A5089F	NOEC = 21.08	2.11[a]	10
Dimethachlor	NOEC = 10	1.00[a]	10
CGA354742	NOEC = 2.02	0.244[d]	8.3
SYN547047	NOEC = 5	0.088[d]	56.8

CGA50266	NOEC = 3.79	0.352[d]	10.8
CGA102935	NOEC = 5	0.088[c]	57
CGA42443	NOEC = 5	0.055[d]	91

[a] Initial PECs
[b] Peak accumulation PECs

Table 196: Assessment of the risk for effects on soil micro-organisms due to the use of A5089H in oilseed rape at 1 x 750 g a.s./ha – BBCH 20

Test substance	NOEC (mg/kg dw)	PEC_{soil} (mg/kg dw)	Ratio of NOEC:PECs
A5089F	NOEC = 21.08	0.421[a]	50
Dimethachlor	NOEC = 10	0.200[a]	50
CGA354742	NOEC = 2.02	0.049[d]	41
SYN547047	NOEC = 5	0.017[d]	294
CGA50266	NOEC = 3.79	0.071[d]	53
CGA102935	NOEC = 5	0.018[c]	278
CGA42443	NOEC = 5	0.011[d]	455

[a] Initial PECs
[b] Peak accumulation PECs

A5089F has no significant effect on soil micro-organisms at 21.08 mg/kg. This is 7.5 times higher than the maximum PEC_S of 2.81 mg A5089H/kg following the worst-case application. A5089F and A5089H are very similar in composition and therefore it is acceptable to read across the result for A5089F to A5089H. For a comparison of the formulations please refer to **Volume 4 – Confidential information.** This indicates that the risk to non-target soil micro-organisms is acceptable following use of A5089H according to the proposed use pattern.

Furthermore, the NOECs for dimethachlor and all metabolites range from 4.8 to 1000 times higher than the maximum soil concentrations indicating an acceptable risk after the use of dimethachlor according to the proposed use pattern.

Non-target higher plants
The risk assessment for non-target higher plants followed the approaches recommended in the EC Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002). For details of the risk assessment, please refer to the Volume 3 – B.9 (CP).

Table 197: TER values for seedling emergence effects of A5089H on non-target plants - ER50 = 42.0 g a.s./ha

Test substance	App. rate	Distance (drift)	Conventional nozzles		50% drift reduction nozzles	
			PER (g a.s./ha)	TER	PER (g a.s./ha)	TER
A5089H	1000 g a.s./ha	1 m (2.77%)	27.7	**1.52**	13.9	**3.0**
		5 m (0.57%)	5.7	7.37	2.85	14.74
	750 g a.s./ha	1 m (2.77%)	20.8	**2.02**	10	**4.04**
		5 m (0.57%)	4.3	9.82	2.1	19.7

TER values for seedling emergence effects are above the trigger of 5 when considering mitigation of either a 5 m no spray buffer or 50% drift reduction.

Table 198: TER values for vegetative vigour effects of A5089H on non-target plants - ER50 >1500 g a.s./ha

Test substance	App. rate	Distance (drift)	Conventional nozzles	
			PER (g a.s./ha)	TER
A5089H	1000 g a.s./ha	1 m (2.77%)	27.7	>54
	750 g a.s./ha	1 m (2.77%)	20.8	>72

The TER values for vegetative vigour effects are above the trigger of 5 for both application rates indicating an acceptable risk following application of A5089H according to the proposed uses.

Soil metabolites of dimethachlor

The studies performed with the dimethachlor metabolites were not considered valid, therefore the endpoint from the studies were not used in the risk assessment.

2.10 ENDOCRINE DISRUPTING PROPERTIES

EXECUTIVE SUMMARY

This document summarises and evaluates all of the available evidence on dimethachlor relevant to the assessment of endocrine disruption, in accordance with the EFSA-ECHA (2018) Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. In order to support Applicants and Competent Authorities, EFSA and ECHA have developed guidance on how to identify endocrine disruptors in accordance with the criteria laid down in Regulation (EC) No 1107/2009. The Guidance Document describes how to gather, evaluate and consider all relevant information for the assessment, conduct a mode of action (MoA) analysis, and apply a weight of evidence approach, in order to establish whether the criteria for the identification of endocrine disruptors laid down in Commission Regulation (EU) 2018/605 of 19 April 2018 amended Annex II to Regulation (EC) No 1107/2009 are fulfilled.

The assessment strategy is based on three conditions stipulated in the ED criteria (adversity, endocrine activity and a biologically plausible link between the two) and the grouping of the parameters described above, as recommended in the EFSA-ECHA Guidance Document.

All available relevant toxicology and ecotoxicology studies for dimethachlor are included in this review. The relevant regulatory mammalian toxicology studies for dimethachlor cover sub-acute, sub-chronic, chronic, developmental and reproductive toxicity studies in a range of mammalian species including rat, mouse, dog and rabbit. The relevant regulatory non-mammalian toxicology studies submitted for dimethachlor cover a range of study types including chronic and reproductive toxicity studies in birds and fish.

The available data on dimethachlor do not indicate effects consistent with endocrine disruption. Thyroid parameters have been sufficiently investigated and the ED criteria are not met for the T modality. However, in accordance with the EFSA-ECHA (2018) Guidance, EAS-mediated parameters have not been sufficiently investigated. Applying this Guidance Document, *in vitro* and *in vivo* mechanistic studies are triggered to further investigate EAS modalities in the absence of a modern two-generation study.

In accordance with the EFSA-ECHA (2018) Guidance, the following *in vitro* and *in vivo* mechanistic studies are triggered for EAS modalities:

1) *In vitro* steroidogenesis assay (OECD 456)
2) *In vitro* ER transactivation assay (OECD 455)
3) *In vitro* AR transactivation assay (OECD 458)
4) Uterotrophic assay (OECD 440)
5) Hershberger assay (OECD 441)

Available ecotoxicology data do not indicate effects consistent with endocrine disruption, however, considering the available data in accordance with the EFSA-ECHA Guidance document (2018), there is not currently a fully adequate dataset to conclude on whether dimethachlor exhibits endocrine disrupting properties in non-target organisms according to the Endocrine Disruption Criteria (2018/605).

To make sufficient data available to reach a conclusion, it was agreed with the applicant to conduct the following studies:

In vivo mechanistic studies (EAS modality)

- 21-day fish screening assay (OECD 230) in the Fathead minnow.

In vivo mechanistic assays to assess T activity against

- Amphibian Metamorphosis Assay (OECD 231)

INTRODUCTION

PURPOSE

This document summarises and evaluates all of the available evidence on dimathachlor to the assessment of endocrine disruption, in accordance with ECHA-EFSA (2018) Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. Following an evaluation of the study reliability, relevance and significance, a weight of evidence assessment is conducted in order to establish whether the criteria are fulfilled.

SCIENTIFIC CRITERIA IN ACCORDANCE WITH REGULATION (EC) NO 1107/2009

Article 23 of Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC necessitates that an active substance "*does not have an inherent capacity to cause endocrine disrupting, neurotoxic or immunotoxic effects*". Consequently, scientific criteria for the determination of endocrine disrupting properties were developed on the basis of the Weybridge[35] and WHO/IPCS definitions[36].

Commission Regulation (EU) 2018/605 of 19 April 2018 amended Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. The criteria state that an active substance, safener or synergist is to be considered as having endocrine disrupting properties that may cause adverse effects on humans, or non-target organisms, if all of the following criteria are met, unless it can be demonstrated that the adverse effects are not relevant to humans or (sub)populations for non-target organisms.

Annex II to Regulation (EC) No 1107/2009 (point 3.6.5) was amended to include the following criteria for endocrine disruption considered relevant humans:

(1) it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences.

(2) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;

(3) the adverse effect is a consequence of the endocrine mode of action

[35] *"an exogenous substance that causes adverse health effect(s) in an intact organism, or its progeny, secondary to changes in endocrine function"* Weybridge Report (EC 1998)

[36] "*an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations*" WHO/IPCS (2002)

Annex II to Regulation (EC) No 1107/2009 (point 3.8.2) was amended to include the following criteria for endocrine disruption in non-target organisms:

(1) it shows an adverse effect in non-target organisms, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;
(2) it has a an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;
(3) the adverse effect is a consequence of the endocrine mode of action

Commission Regulation (EU) 2018/605 stipulates that the identification of endocrine disruptors shall be based on all available relevant scientific data, and that the relevance, quality, consistency and coherence of should be considered. Adverse effects that are non-specific secondary consequences of other toxic effects shall not be considered for the identification of the substance as endocrine disruptor.

EFSA-ECHA (2018) GUIDANCE DOCUMENT

In order to support Applicants and Competent Authorities, the European Commission asked the European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA) to develop guidance on how to identify endocrine disruptors in accordance with the criteria laid down in Regulation (EC) No 1107/2009. The Guidance Document describes how to gather, evaluate and consider all relevant information for the assessment, conduct a mode of action (MoA) analysis, and apply a weight of evidence (WoE) approach, in order to establish whether the criteria are fulfilled (ECHA/EFSA 2018).

In order to determine whether a substance causes adverse effect(s) that can be plausibly linked to endocrine activity, all relevant information needs to be collected, assessed and grouped in accordance with the guidance. The rationale for grouping is loosely based on OECD Guidance and the Joint Research Centre (JRC) screening methodology to identify potential disruptors of estrogenic, androgenic, thyroidal and steroidogenic (EATS) modalities (JRC 2016).

The OECD Guidance Document 150 lists the test guidelines and parameters that are considered relevant when investigating the ED properties of a substance (OECD 2018). In the context of this guidance, all the parameters listed by the OECD GD 150 (Table 2.1 and Table 2.2) are grouped into four groups:

- ***In vitro* mechanistic**: Parameters measured *in vitro* that provide information on the mechanism through which a substance could be considered endocrine active (OECD CF level 2).

- ***In vivo* mechanistic**: Parameters measured *in vivo* that provide information on endocrine activity that are usually not considered adverse (OECD CF level 3).

- **EATS mediated:** Parameters measured *in vivo* that may contribute to the evaluation of adversity, which may also be indicative of an EATS MoA (OECD CF level 4 and 5).

- **Sensitive to, but not diagnostic of EATS:** Parameters measured *in vivo* that may contribute to the evaluation of adversity, however, these effects cannot be considered diagnostic for any one of the EATS modalities.

Assessment strategy

The assessment strategy is based on the three conditions stipulated in the ED criteria (adversity, endocrine activity and a biologically plausible link between the two) and the grouping of the parameters described above, as

recommended in the ECHA-EFSA (2018) Guidance. The assessment strategy is applicable to both humans and non-target organisms, and is illustrated in Figure 2.1. The remainder of this report is structured as follows:

Section 3: Gather information & assess the evidence
Section 4: Data reviews
Section 5: Integration and assessment of lines of evidence
Section 6: Initial analysis of the evidence (WoE)
Section 7: MoA analysis
Section 8: Conclusion on the ED criteria.

Following an outline of the methodology to evaluate reliability and relevance (Section 3), the data reviews in Section 4 are organised around the OECD's Conceptual Framework for the Testing and Assessment of Endocrine Disrupting Chemicals (Table 2.1 and Table 2.2). In accordance with the Guidance (ECHA/EFSA 2018), data from the various Conceptual Framework levels have differing applications and implications, e.g. providing mechanistic information (Levels 2 and 3) or providing data on adverse effects on endocrine relevant endpoints (Levels 4 and 5). Section 5 integrates and assesses the lines of evidence, whereas Section 6 evaluates all of the available evidence in a weight of evidence assessment, considering the availability of "EATS mediated" parameters. Where EATS mediated parameters are not sufficiently investigated according to the ECHA-EFSA Guidance (2018), potential endocrine modalities and testing strategies are outlined in Section 7. Section 8 provides a conclusion on the ED criteria.

Each Section considers effects relevant to both human health and non-target organisms. It should be noted that non-EATS modalities and potential for endocrine disrupting properties in invertebrate organisms are not currently within the scope of the Guidance (EFSA-ECHA 2018).

Table 199: OECD Conceptual Framework for Testing and Assessment of Endocrine Disruptors

Level 1 Existing data and non-test information	• Physical & chemical properties, e.g., MW reactivity, volatility, biodegradability. • All available toxicological data from standardized or non-standardized tests. • Read across, chemical categories, QSARs and other *in silico* predictions, and ADME model predictions.
Level 2 *In vitro* assays providing data about selected endocrine mechanism(s)/pathways(s)	• Estrogen or androgen receptor binding affinity • Estrogen receptor transactivation (OECD TG 455) • Androgen or thyroid transactivation (If/when TGs are available) • Steroidogenesis in vitro (OECD TG 456) • MCF-7 cell proliferation assays (ER ant/agonist) • Other assays as appropriate
Level 3 – Mammalian Species *In vivo* assays providing data about selected endocrine mechanism(s)/pathway(s)	• Uterotrophic assay (OECD TG 440) • Hershberger assay (OECD TG 441)
Level 4 – Mammalian Species *In vivo* assays providing data on adverse effects on endocrine relevant endpoints	• Repeated dose 28-day study (OECD TG 407) • Repeated dose 90-day study (OECD TG 408) • 1-generation reproduction toxicity study (OECD TG 415) • Male pubertal assay (see GD 150 Chapter C4.3) • Female pubertal assay (see GD 150 Chapter C4.4) • Intact adult male endocrine screening assay (see GD 150 Chapter Annex 2.5) • Prenatal developmental toxicity study (OECD TG 414) • Chronic toxicity and carcinogenicity studies (OECD TG 451-3) • Reproductive screening test (OECD TG 421 if enhanced) • Combined 28-day/reproductive screening assay (OECD TG 422 if enhanced) • Developmental neurotoxicity (OECD TG 426)
Level 5 – Mammalian Species *In vivo* assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the life cycle of the organism	• Extended one-generation reproductive toxicity study (OECD TG 443) • 2-Generation reproduction toxicity study (OECD TG 416)
Level 3 – Non-Mammalian Species *In vivo* assays providing data about selected endocrine mechanism(s)/pathway(s)	• Xenopus embryo thyroid signalling assay (When/if TG is available) • Amphibian metamorphosis assay (OECD TG 231) • Fish Reproductive Screening Assay (OECD TG 229) • Fish Screening Assay (OECD TG 230) • Androgenized female stickleback screen (GD 140)
Level 4 – Non-Mammalian Species	• Fish sexual development test (OECD TG 234) • Fish Reproduction Partial Lifecycle Test (when/If TG is Available)

In vivo assays providing data on adverse effects on endocrine relevant endpoints	• Larval Amphibian Growth & Development Assay (when TG is available) • Avian Reproduction Assay (OECD TG 206) • Mollusc Partial Lifecycle Assays (when TG is available) • Chironomid Toxicity Test (TG 218-219) • *Daphnia* Reproduction Test (with male induction) (OECD TG 211) • Earthworm Reproduction Test (OECD TG 222)* • Enchytraeid Reproduction Test (OECD TG 220) • Sediment Water *Lumbriculus* Toxicity Test Using Spiked Sediment (OECD TG 225) 4 • Predatory mite reproduction test in soil (OECD TG 226)* • Collembolan Reproduction Test in Soil (TG OECD 232)* *: Studies performed on formulated product
Level 5 – Non-Mammalian Species *In vivo* assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the life cycle of the organism	• FLCTT (Fish LifeCycle Toxicity Test) (when TG is available) • Medaka Multigeneration Test (MMGT) (when TG is available) • Avian 2 generation reproductive toxicity assay (when TG is available) • Mysid Life Cycle Toxicity Test (when TG is available) • Copepod Reproduction and Development Test (when TG is available) • Sediment Water Chironomid Life Cycle Toxicity Test (TG 233)

Note: These lists are not exhaustive.

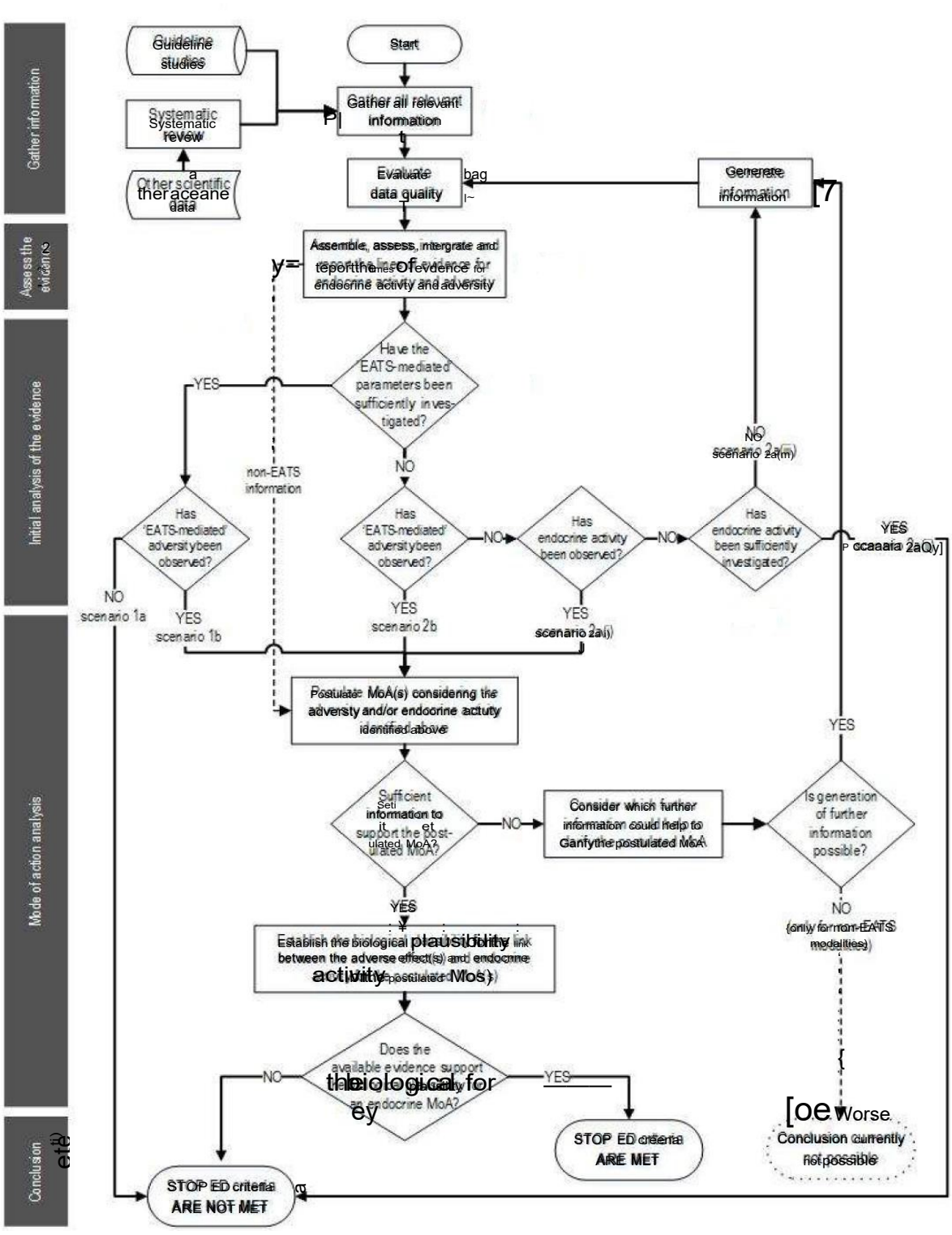


Figure 2.10-1. Flow Chart illustrating the assessment strategy for evaluating ED properties according the EFSA-ECHA (2018) Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (reproduced from Figure 1 therein).

GATHER INFORMATION & ASSESS THE EVIDENCE

Gather information

In this step all available relevant information is gathered both in terms of regulatory studies conducted in accordance with internationally agreed study protocols, and peer-reviewed published literature retrieved with systematic review methodology.

Regulatory studies

The available relevant regulatory *in vitro* toxicology studies submitted for dimethachlor are included in this review.

The relevant regulatory mammalian toxicology studies submitted for dimethachlor cover a range of study types including sub-acute, sub-chronic, chronic, developmental and reproductive toxicity studies in a range of mammalian species including rat, mouse, dog and rabbit.

The relevant regulatory non-mammalian toxicology studies submitted for dimethachlor cover a range of study types including chronic and reproductive toxicity studies in birds and fish.

Open scientific literature

A series of comprehensive searches of the open scientific literature were undertaken for the Annex 1 renewal submission in accordance with **EFSA guidance document (EFSA Journal 2011;9(2):2092)** (full details can be found in MCA Section 9 of the dossier). Any relevant and reliable data from this search have also been considered in this review.

A more extensive search has also been conducted using more specific endocrine disruption search terms and an extended duration to ensure that all available literature have been located. This additional search was carried out to identify *in vitro* and *in vivo* studies designed to assess the effects of dimethachlor on the endocrine system. Full details are provided in Appendix 1 and the search terms are provided in Appendices 2, 3 and 4. The additional search identified no papers.

Assess the evidence

Information shall be evaluated for its relevance and reliability. Evaluation of each of the relevant studies was based on the framework developed by the European Chemical Industry Council (CEFIC) Endocrine Modulators Steering Group (EMSG) for the weight of the evidence evaluation of potential endocrine disrupting substances (CEFIC, 1999). This framework consists of an independent assessment of a study's reliability and relevance, from which an overall assessment of the study's significance, relative to other studies using the same substance, is then derived**.**

Study reliability

Defined as '*the inherent quality of a test report or publication relating to preferably standardised methodology and the way the experimental procedure and results are described to give clear evidence of the clarity and plausibility of findings'* (Klimisch *et al*. 1997). In accordance with the ECHA-EFSA (2018) Guidance, the reliability of the studies was assessed based on the criteria described by Klimisch *et al*. (1997), Brown *et al*. (2001), and CEFIC (1999). Each study was assigned to one of four categories on the basis of compliance with the criteria, as follows:

- **Reliable without restrictions** – studies conducted according to testing guidelines (preferably Good Laboratory Practice [GLP]) or in which all of the criteria are fully documented and reported.

- **Reliable with restrictions** – studies that do not follow broadly accepted testing guidelines, but that document and report compliance with a substantial majority of the criteria.
- **Not reliable** – studies in which there are notable deficiencies in scientific integrity (e.g. interferences between the measuring system and the test substance) or that document and report compliance with relatively few of the criteria.
- **Not assignable** – usually reserved for abstracts, secondary literature, subject reviews or book reviews.

Klimisch reliability codes 1 and 2 are equivalent to CEFIC EMSG "High" and "Medium" confidence of repeatability. Klimisch reliability code 3 is equivalent to CEFIC EMSG "Low" confidence of repeatability.

Study relevance

Data relevance refers to the appropriateness of the data for the intended purpose of the assessment (EFSA 2015; Vermeire *et al*. 2013). Relevance assessment differentiates between the various endpoints reported to be influenced by endocrine disrupting substances on the basis of mechanistic evidence and observed effects. Some reported endpoints are more explicitly the consequence of an endocrine disrupting mechanism than others. Using the criteria developed by CEFIC EMSG it is possible to establish a hierarchy of endpoint relevance as follows:

- Observed adverse health effects with mechanistic support to establish causal linkage.
- Observed health effects with limited understanding of mechanism.
- Biomarker of exposure.
- Mechanistic potential with no observed effect.

CEFIC EMSG assigns the relevance of *in vitro* and *in vivo* studies as High, Medium or Low according to the criteria detailed in Tables 200 and 201, respectively. Note that these criteria are not exhaustive and in some cases (e.g. unusual study designs), relevance may be assigned according to different criteria.

Table 200: Relevance of *In Vivo* Assays According to CEFIC EMSG

Relevance	Description
High	• Endpoint is based upon receptor binding potential coupled with transcriptional activation in a whole cell or subcellular assay. • Receptor binding potential in a whole cell assay. • Assessment of steroid metabolism in a whole cell assay.
Medium	• Endpoint is based on receptor binding activity in a subcellular assay. • Endpoint is based on cell growth or other endpoint, not a direct measurement of receptor mediated activity. • Endpoint of steroid metabolism in a subcellular assay.
Low	• Not applicable; all *in vitro* assays are relevant to at least some extent by definition.

Table 201: Relevance of *In Vivo* Assays/Endpoints According to CEFIC EMSG OECD

Relevance	Description
High	• Endpoint(s) in a multi-generational test or other repeat dose toxicity test that is specifically controlled by the endocrine system.

Relevance	Description
	• Parallel dose-response changes in hormone levels in the presence of consequent toxicological effects (mammalian only). • Negative data from a short term/screening assay specifically controlled by the endocrine system.
Medium	• Endpoint in a multi-generation test, or other repeat dose standard toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity, etc. • Positive endpoint data from a short-term/screening assay specifically controlled by the endocrine system. • Changes in hormone levels in the absence of any toxicological changes (mammalian only).
Low	• Evidence indicates that the endpoint is not controlled by the endocrine system.

In accordance with the EFSA-ECHA (2018) guidance, when evaluating the relevance of studies conducted according to outdated guidelines, it is important to consider what parameters relevant for identification of ED properties were included in the study design. Missing parameters with respect to the updated version of the test guidelines are clearly reported.

Study significance

According to the CEFIC EMSG framework, the "weight" or significance that should be assigned to a study is derived from a combination of its reliability/repeatability and relevance scores. It is a measure of the significance which can be ascribed to a study in reaching a conclusion about endocrine disruption. It is also the parameter which is ultimately used in the evaluation of the endocrine disrupting potential for the combined dataset for a particular substance. CEFIC EMSG assigns the significance of *in vitro* and *in vivo* studies as High, Indicative, Low or Unusable according to the criteria detailed in Tables 202 and 203, respectively. Note that these criteria are not exhaustive and in some cases (e.g. unusual study designs), significance may be assigned according to different criteria.

Table 202: Significance of *In Vitro* Assays According to CEFIC EMSG

Significance	Description
Indicative[1]	• Studies of high relevance and with reliability scores of 1.
Low	• Studies of medium relevance and with reliability scores of 1. • Studies of high relevance and with reliability scores of 2.
Unusable	• Data from studies with reliability scores of 3 or 4.

[1] The CEFIC EMSG framework does not allow for *in vitro* studies to be classified as High significance. At best these can only be "indicative" of mechanistic potential. However, a negative result of "Indicative" significance is sufficient to be definitive for the mechanism being investigated.

Table 203: Significance of *In Vivo* Assays According to CEFIC EMSG

Significance	Description
High	• Repeat dose studies of high relevance and with reliability scores of 1 or 2.
Indicative	• Screening assay studies of high relevance and with reliability scores of 1 or 2. • Repeat dose studies of medium relevance and with reliability scores of 1 or 2.
Low	• Screening assay studies of medium relevance and with reliability scores of 1 or 2.
Unusable	• Data from studies with reliability scores of 3 or 4.

The final step in the CEFIC EMSG framework, and Section 4 of this document weighs the balance of evidence from the significance assessments of all the studies evaluated. This weight of the evidence evaluation is consistent with the general approach proposed in the ECHA-EFSA (2018) Guidance and OECD Guidance Document No. 150 (OECD, 2018). As described in tables 202 and 203, studies with a reliability score of 3 - Not reliable or 4 - Not assignable, will not be included in this review.

DATA REVIEWS

This section assembles all the lines of evidence for endocrine activity and adversity. Following the OECD Conceptual Framework and the four groupings specified in the ECHA/EFSA (2018) Guidance, the lines of evidence are organised according to their contribution to their assessment. The available data for dimethachlor has been compiled using the spread sheet recommended by the EFSA-ECHA (2018) Guidance (appendix E in that document), and is supplied alongside this report.

IN SILICO STUDIES IN OECD CONCEPTUAL FRAMEWORK LEVEL 1
No *in silico* mechanistic data in OECD conceptual framework level 1 was identified for inclusion in this review.

IN SILICO STUDIES IN OECD CONCEPTUAL FRAMEWORK LEVEL 1
No *in vitro* mechanistic data in OECD conceptual framework level 2 was identified for inclusion in this review.

IN VIVO DATA – MAMMALIAN SPECIES

Short term studies in OECD Conceptual Framework level 3

No *in vivo* mechanistic data in OECD conceptual framework level 3 was identified for inclusion in this review.

Short term studies in OECD Conceptual Framework level 4

Report:	[redacted] (1993d). 28-day repeated dose dermal toxicity study in the rat. Test No. 921090. [redacted]. Unpublished report. Syngenta file: CGA1702/0208.

Guidelines: OECD 410 (1981)

GLP: Yes

Study design: Groups of five male and five female albino rats (Tif: RAIf) were dermally administered dimethachlor at dose levels of 0, 10, 100 or 1000 mg/kg bw on a 5 day/week basis for a period of four weeks. The test material was applied to the shaved back skin (approximately 10% of body surface) of the rats under occlusive dressing. The test material was dissolved in 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80. The test material or vehicle solution was evenly dispersed on a gauze pad, which was applied to the clipped skin, loosely covered with aluminium foil and fastened to the body with tape. The control animals received the vehicle solution. The animals were exposed for 6 hours/day. After each application, the dressing was removed, and the exposed area cleaned with water. Clinical signs, body weight and food intake were monitored. Blood samples were taken for laboratory investigations at the end of the treatment period. All animals were killed at the end of the treatment period and any macroscopic changes noted. Specified organs were weighed, and selected tissues removed for histopathological examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations.
- Organ weights: adrenals, ovaries, testes.
- Histopathological examination: thymus, thyroid with parathyroid, spleen

Deviations from current guideline: Relative to the current guideline, the tissues preserved for histopathological examination were limited and no histopathological examination of the relevant organs was undertaken. There were no deviations considered to compromise the scientific validity of the study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

A statistically significant increase in absolute (+23.6%) adrenal weight and adrenal to bodyweight ratio (+28.7%), in addition to decreased absolute testes weight (-9.7%) was reported in low dose males. An increase in absolute ovary weights in females at the lowest (+30.4%) and highest (+28.9%) dose groups was also reported. In the absence of a clear dose-response relationship these changes are not considered toxicologically relevant or related to dimethachlor treatment.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/no effects observed).

Report:	[redacted] (1992a). 4-week oral toxicity (feeding) study in the rat. Test No. 921024. [redacted]. Unpublished report. Syngenta file: CGA17020/0179

Guidelines: OECD 407 (1981)

GLP: Yes

Study design: Groups of ten male and ten female albino rats (HanIBM:WIST SPF) were administered dimethachlor via the diet at inclusion dose levels of 0, 100, 700, 3000 or 5000 ppm for a period of four weeks (equivalent to 0, 9.50, 66.98, 294.81 and 487.93 mg/kg/day for males and 0, 9.96, 68.27, 303.99 and 485.17 mg/kg/day for females, respectively). The test material was formulated into the diet every two weeks and was

made available to the rats *ad libitum,* seven days/week, for the duration of the study period. The control animals received untreated diet. Clinical signs, body weight and food intake were monitored. Blood samples were taken for laboratory investigations at the end of the treatment period. All animals were killed at the end of the treatment period and any macroscopic changes noted. Specified organs were weighed, and selected tissues removed for histopathological examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations.
- Organ weights: adrenals, testes.
- Histopathological examination: adrenals, epididymides, mammary gland, ovaries, thyroid and parathyroid gland, pituitary, prostate, seminal vesicles, testes, thymus, uterus, vagina.

Deviations from the current guideline: The OECD 407 guideline was updated on 3 October 2008, to include endocrine organs, vaginal lavage at necropsy (i.e. oestrous cycle staining) and optional thyroid hormone measurements (T3, T4 and TSH). None of the deviations are considered to have affected the validity of this GLP and Guideline compliant study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/no effects observed).

Report:	[redacted] (1993). 28-day oral cumulative toxicity study in rats (gavage). Test No. 921091. [redacted]. Unpublished report. Syngenta File: CGA17020/0207

Guidelines: OECD 407 (1981)

GLP: Yes

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations.
- Organ weights: adrenals, ovaries, testes.
- Histopathological examination: testes, epididymides, adrenals.

Deviations from the current guideline: The OECD 407 guideline was updated on 3 October 2008, to include endocrine organs, vaginal lavage at necropsy (i.e. oestrous cycle staining) and optional thyroid hormone measurements (T3, T4 and TSH). A limited number of organs were examined at the terminal necropsy, omitting histological examination of the thyroid and parathyroid, pituitary, ovaries and mammary tissues. None of the deviations are considered to have affected the validity of this GLP and Guideline compliant study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

The testes of 3/10 male rats of group 4 (750 mg/kg/day), which were terminated on days 2 and 5 of treatment, presented with minimal to moderate reduction of spermatogenesis. This lesion was characterised by a reduction of mature spermatozoa and degenerating germinal cells in the tubular lamina. These changes occurred alongside marked systemic toxicity, including bodyweight weight loss, reduced food intake, clinical observations (hunched posture, hypoactivity and piloerection) and mortality. The reduced spermatogenesis in premature decedents was likely to be associated with the body weight gain reduction (-25%) and reduced food intake (-26%) observed in males treated at 750 mg/kg/day. Males that survived to scheduled termination did not present any testicular changes (750/350 mg/kg/day). As this effect in the testis was only observed in premature decedents during the first few days of the study this is considered to be the result of severe systemic toxicity.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/effects observed).

Report:	[redacted] (1994). 3-month oral toxicity study in rats (dietary). Test No. 931117. [redacted]. Unpublished report. Syngenta file: CGA17020/0265

Guidelines: OECD 408 (1981)

GLP: Yes

Study design: Groups of ten male and ten female albino rats (Tif:RAIf SPF, Sprague-Dawley derived) were administered dimethachlor by dietary inclusion at dose levels of 0, 30, 1000 or 6000 ppm (equivalent to 0, 2.21, 71.7 and 449 mg/kg/day in males and 0, 2.21, 76.0 and 457 mg/kg/day in females) for a period of thirteen weeks. An additional ten animals per sex were included in the control and high dose level groups, which were maintained on untreated diet for an additional 4-week period in order to assess recovery from any effects. The test material was formulated freshly each day, and the control animals received untreated diet alone in the same way. Clinical signs, body weight and food intake were frequently monitored. Blood and urine samples were taken for laboratory investigations at the end of the treatment period. All animals were killed at the end of the treatment period and any macroscopic changes noted. Specified organs were weighed and selected tissues removed for histopathological examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations.
- Organ weights: adrenals, ovaries, testes, thyroid.
- Histopathological examination: testes, epididymides, uterus, vagina, ovaries, pituitary, adrenals, thyroid with parathyroid.

Deviations from the current guideline: The OECD 408 guideline was updated on 25 June 2018, to include thyroid hormones (T4, T3 and TSH), sperm parameters and vaginal cytology, none of which were considered. A limited number of organs were examined at the terminal necropsy, omitting epididymis, prostate and seminal vesicle weights and histological examination of the cervix, mammary gland, pituitary, prostate and seminal vesicles. No investigation of sensory activity, grip strength or motor activity were performed. None of the deviations are considered to have affected the validity of this GLP and Guideline compliant study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Increased testes weights (relative to body weight) were recorded for males at 6000 ppm ($p<0.05$). However, the absolute testes weights were similar to controls. In the high dose group (6000 ppm), a depressed bodyweight development resulted in cumulative bodyweight gains 18.2% lower than in control males. By the end of the treatment period, mean values for males were 14% lower than in the respective control group. As such these changes in relative, but not absolute, testis weight are considered to be secondary to reduced body weight.

The incidence of testicular tubular atrophy was 1, 1, 0, 1 across, 0, 30, 1000 or 6000 ppm groups, respectively. This finding was also noted in two control animals at the recovery period kill. The testicular tubular atrophy was also associated with reduced spermatogenesis in two of the males. The changes in the testes were inconsistent and also showed no dose-concordance. An increased incidence of fatty change in the adrenal cortex was reported for males treated at 1000 ppm. In the absence of a dose-response, the findings in the testes and adrenals were not considered related to dimethachlor treatment.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/ effects observed).

Report:	[redacted] (1992b). 4-week oral toxicity (feeding) study in the mouse. Test No. 921032. [redacted]. Unpublished report. Syngenta file: CGA17020/0178

Guidelines: OECD 407 (1981)

GLP: Yes

Study design: Groups of ten male and ten female mice (HanIBM:NMRI SPF) were administered dimethachlor via the diet at inclusion dose levels of 0, 100, 1000, 3000 or 7000 ppm for a period of four weeks (equivalent to 0, 20.9, 204.4, 623.7 and 1493.3 mg/kg/day for males and 0, 23.2, 232.3, 715.2 and 1783.7 mg/kg/day for females, respectively). The test material was formulated into the diet every two weeks and was made available to the mice *ad libitum,* seven days/week, for the duration of the study period. The control animals received untreated diet. Clinical signs, body weight and food intake were frequently monitored. Blood samples were taken for laboratory investigations at the end of the treatment period. All animals were killed at the end of the treatment period and any macroscopic changes noted. Specified organs were weighed, and selected tissues removed for histopathological examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations.
- Organ weights: adrenals, testes.
- Histopathological examination: adrenals, epididymides, mammary gland, ovaries, thyroid and parathyroid gland, pituitary, prostate, seminal vesicles, testes, thymus, uterus, vagina.

Deviations from the current guideline: The OECD 407 guideline was updated on 3 October 2008, to include endocrine organs, vaginal lavage at necropsy (i.e. oestrous cycle staining) and optional thyroid hormone

measurements (T3, T4 and TSH). Limited organ weights were recorded, but microscopic assessment was conducted on most relevant organs. None of the deviations are considered to have affected the validity of this GLP and Guideline compliant study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/no effects observed).

Report:	[redacted] (1999). 3-month range-finding oral toxicity study in mice (dietary). Test No. 981115. [redacted]. Unpublished report. Syngenta file: CGA17020/0505

Guidelines: OECD 408 (1981)

GLP: Yes

Study design: Groups of ten male and ten female albino mice (ICO:CD1 Crl) were administered dimethachlor by dietary inclusion at dose levels of 0, 100, 3 500 or 7 000 ppm (equivalent to 0, 17.5, 175, 614 and 1 228 mg/kg/day in males and 0, 18.5, 185, 648 and 1 296 mg/kg/day in females) for a period of thirteen weeks. The test material was formulated at approximately monthly intervals and the control animals received untreated diet alone in the same way. Clinical signs, body weight and food intake were frequently monitored. Blood samples were taken for laboratory investigations at the end of the treatment period. All animals were killed at the end of the treatment period and any macroscopic changes noted. Specified organs were weighed, and selected tissues removed for histopathological examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations.
- Organ weights: adrenals, ovaries, testes, epididymides, thyroid.
- Histopathological examination: testes, epididymides, ovaries, adrenals, thyroid with parathyroid.

Deviations from the current guideline: The OECD 408 guideline was updated on 25 June 2018, to include thyroid hormones (T4, T3 and TSH), sperm parameters and vaginal cytology, none of which were considered. A limited number of organs were examined at the terminal necropsy, omitting uterus, prostate and seminal vesicle weights and histological examination of the uterus, vagina, cervix, mammary gland, pituitary, prostate and seminal vesicles. No investigation of sensory activity, grip strength or motor activity were performed. None of the deviations are considered to have affected the validity of this GLP and Guideline compliant study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

A slight increase in thyroid weights (absolute and relative to body weight) was reported in females treated with 1000, 3500 or 7000 ppm (+15.0%, +18.7% and +16.3% relative to bodyweight, respectively). In the absence of a

dose-response relationship, statistical significance and a histopathological correlate, the increase in thyroid weights were not considered toxicologically relevant.

Significantly increased absolute and relative liver weights were reported for males at 1000, 3500 and 7000 ppm by 24%/12%, 22%/17% and 24%/27%, respectively. A corroborative increase in the incidence of hepatocyte hypertrophy was reported in males; the incidence across groups was 3, 7, 7 and 9 at 0, 1000, 3500 and 7000 ppm, respectively. In females at 3500 and 7000 ppm absolute and relative liver weights were 15%/10% and 28%/27% above the respective control values. Histological correlates were noted, with an increase incidence of hepatocyte hypertrophy noted at 3500 ppm (9/10) and 7000 ppm (10/10) when compared with the control group (3/10).

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/effects observed).

Report:	[redacted] (1993). 28-day range finding toxicity study in beagle dogs. Test No. 921193 [redacted]. Unpublished report. Syngenta file: CGA17020/0220

Guidelines: None.

GLP: No.

Study design: Groups of two beagle dogs of each sex were treated with dimethachlor at dietary inclusion levels of 500, 2000 or 4000 ppm for 28 days, which was calculated to be equivalent to a mean daily intake of 15.3, 63.0, or 120 mg/kg bw/day for males and 18.1, 70.2, or 119 mg/kg bw/day for females. The control group received untreated diet. The dogs were 26 to 29 weeks old at the initiation of treatment. Laboratory investigations were carried out on all animals during the pre-test period and at week 4. All animals were sacrificed at termination of the study after week 4 and complete necropsies were performed. Specified organs were weighed and selected tissues were examined histopathologically.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic examinations.
- Organ weights: adrenals, ovaries, testes, thyroid with parathyroid.
- Histopathological examination: adrenals, ovaries, testes, thyroid with parathyroid.

Deviations from current guideline: The study design of this range-finder was broadly comparable to OECD 409 (1981). However, the group size (2/sex/dose), exposure duration (28-days) and tissue lists for macro- and microscopic assessment were limited relative to the current guideline. These deviations are not considered to affect the validity of this range-finding study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Statistically significant increases in absolute ovary weight (+27%) were noted at the mid-dose group ($p<0.05$), in addition to increased relative ovary weights at the mid (+34.8%) and high (+33.3%) dose groups. These findings were not observed in the subsequent 90-day study, and in the absence of a histopathological correlate, were not considered related to dimethachlor treatment.

An increased number of developmental cysts in the parathyroid gland were noted in high dose males. However, this is a common occurrence in this strain of Beagle dogs, and due to the developmental nature of the lesion, it cannot be attributed to dimethachlor treatment.

Minimal focal tubular atrophy of the testis was observed in one of the high dose males. This finding occurs spontaneously in Beagle dogs and was not attributed to dimethachlor treatment. These equivocal changes were observed at dose levels showing marked systemic toxicity, manifest as reduced body weight gain, food intake and hepatotoxicity.

CONCLUSIONS

Reliability score	**2** - Reliable with restriction. Range finding study with reduced numbers of animals (only two animals per sex).
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/effects observed).

Report:	[redacted] (1994). 3-month dietary toxicity study in beagle dogs. Test No. 921194. [redacted]. Unpublished report. Syngenta file: CGA17020/0266

Guidelines: OECD 409 (1981); MAFF NohSan No. 4200 (1985)

GLP: Yes

Study design: Groups of four Beagle dogs of each sex were treated with dimethachlor at dietary inclusion levels of 300, 1000 or 3000 ppm for three months. The calculated mean daily intake was 9.96, 32.3 or 104 mg/kg bw/day for males and 10.8, 36.0 or 103 mg/kg bw/day for females. The control group received the same diet without the addition of dimethachlor. The dogs were 23 to 30 weeks old at the initiation of treatment. Laboratory investigations were carried out on all animals during the pre-test period and at weeks 7 and 13. All animals were sacrificed at termination of the study and complete necropsies were performed. Specified organs were weighed and selected tissues were examined histopathologically.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic examinations.
- Organ weights: adrenals, ovaries, testes, thyroid with parathyroid.
- Histopathological examination: mammary area, adrenals, prostate, epididymis, testes, vagina, uterus, ovaries, pituitary gland, thyroid with parathyroid.

Deviations from the current guideline: The OECD 409 guideline was updated on 21 September 1998, recommending at least 4 animals/sex/dose, with additional satellite groups for any intercurrent kills. There are no significant deviations and the [redacted] (1994) study is considered equivalent to the current OECD 409 (1998) guideline.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Tubular atrophy in the testis in one of the two males was observed at the low-dose group together with epididymal inflammatory cell infiltration. A common finding in the colony of Beagle dogs and in the absence of dose concordance, this was not considered treatment related.

Uterine atrophy was noted in one female at the high dose, however, this equivocal change was noted at dose levels showing marked systemic toxicity, manifest as significant reductions in body weight gain, food intake and hepatotoxicity.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction.
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/no effects observed).

Report:	[redacted]. (1974). 90-Day dietary toxicity study in dogs. Test No. [redacted]. [redacted]. Unpublished report. Syngenta file: CGA17020/0112

Guidelines: OECD 409 (1981)

GLP: No

Study design: Groups of four Beagle dogs of each sex were treated with dimethachlor at dietary inclusion levels of 100, 350 or 1250 ppm for three months. The calculated mean daily intake was 3.4, 10.1 or 35.4 mg/kg bw/day for males and 3.1, 10.4 or 45.4 mg/kg bw/day for females. The control group received the same diet without the addition of dimethachlor. An additional one male and one female from the control and high dose level groups were included to assess potential recovery over a 4-week off-dose period at the end of the treatment period. The dogs were approximately 24 to 42 weeks old at the initiation of treatment. Laboratory investigations were carried out on all animals during the pre-test period and at weeks 5, 9 and 13 and at the end of the recovery period. All identified animals were sacrificed at termination of the two phases of the study and complete necropsies were performed. Specified organs were weighed and selected tissues were examined histopathologically.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic examinations.
- Organ weights: adrenals, ovaries, testes, pituitary, thyroid with parathyroid.
- Histopathological examination: mammary gland, adrenals, prostate, epididymis, testes, vagina, uterus, ovaries, pituitary gland, thyroid with parathyroid.

Deviations from the current guideline: The OECD 409 guideline was updated on 21 September 1998, recommending at least 4 animals/sex/dose, with additional satellite groups for any intercurrent kills. The ([redacted] study was conducted prior to the enactment of OECD Test Guidelines, consequently, the laboratory parameters and organs examined at terminal necropsy were limited.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction.
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).

Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/no effects observed).

Chronic and carcinogenicity studies in OECD Conceptual Framework level 4

Report:	[redacted] (1995). 24-month carcinogenicity and chronic toxicity study in rats (dietary). Test No. 921064. [redacted]. Unpublished report. Syngenta file: CGA17020/0301.

Guidelines: OECD 453 (1981)

GLP: Yes

Study design: Groups of eighty male and eighty female albino rats (Tif:RAIf SPF, Sprague-Dawley derived) were administered dimethachlor by dietary inclusion at dose levels of 0, 20, 300 or 4000 ppm (equivalent to 0, 0.765, 11.1 and 157 mg/kg/day in males and 0, 0.892, 12.9 and 183 mg/kg/day in females) for a period of twenty-four months. A total of 50 animals/sex/group were designated for evaluation of carcinogenicity, an additional 20 animals/sex/group for provision of blood and urine samples during the study and an additional 10 animals/sex/group for interim sacrifice after 12 months of treatment. The test material was formulated at 4-week intervals throughout the study and the control animals received untreated diet alone in the same way. Clinical signs, body weight and food intake were frequently monitored. Blood and urine samples were taken for laboratory investigations at intervals during the study (Weeks 13, 26, 52, 78 and 105). All designated animals were killed at the end of the scheduled interim and terminal treatment periods and any macroscopic changes noted. Specified organs were weighed, and selected tissues removed for histopathological examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations.
- Organ weights: adrenals, ovaries, testes.
- Histopathological examination: mammary gland, prostate, seminal vesicles, testes, epididymides, uterus, vagina, ovaries, pituitary gland, thyroid with parathyroid.

Deviations from the current guideline: Relative to OECD 453 (2018), the number and sizing of groups, in addition to the dose levels and frequency was acceptable. However, the study omitted organ weights of the epididymides, thyroid (weighed post-fixation with parathyroids) and uterus. The dose level spacing was larger than recommended (10-fold rather than 4-fold) and the clinical examinations were limited. The minor deviations are not considered to affect the validity of this GLP and Guideline compliant study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

A statistically significant ($p<0.05$) decrease in absolute adrenal weights for females treated with 4000 or 300 ppm (-21% and -9%, respectively) at the 24-month terminal kill, however, these were within historical control values and in the absence of a histopathological correlate, were not considered treatment-related.

An increase in the number of high dose males with fluid contents of the testicular tunica albuginea and testicular tubular atrophy was noted relative to controls. These macroscopic and microscopic testicular findings were considered to reflect spontaneous, age-related change occurring in the colony of rats used in the study.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction

Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/effects observed).

Report:	[redacted] (2001). 18-month oncogenicity study in mice (dietary). Test No. 991036. [redacted]. Unpublished report. Syngenta file: CGA17020/0583.

Guidelines: OECD 451 (1981)

GLP: Yes

Study design: Groups of seventy male and seventy female albino mice (ICO:CD1 Crl)) were administered dimethachlor by dietary inclusion at dose levels of 0, 20, 300, 1500 or 4000 ppm (equivalent to 0, 2.54, 34.3, 184 and 511 mg/kg/day in males and 0, 2.25, 31.4, 162 and 454 mg/kg/day in females) for a period of eighteen months. A total of 50 animals/sex/group were designated for evaluation of carcinogenicity, an additional 10 animals/sex/group for provision of blood samples for haematological assessment during the study and an additional 10 animals/sex/group for interim sacrifice after 9 months of treatment. The test material was formulated at approximately 4-week intervals throughout the study and the control animals received untreated diet alone in the same way. Clinical signs, body weight and food intake were frequently monitored. Blood samples were taken for laboratory investigations at intervals during the study (Weeks 40 and 79). All designated animals were killed at the end of the scheduled interim and terminal treatment periods and any macroscopic changes noted. Specified organs were weighed, and selected tissues removed for histopathological examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations.
- Organ weights: adrenals, ovaries, testes.
- Histopathological examination: adrenal glands, epididymides, mammary gland, ovaries, parathyroid gland, pituitary gland, prostate gland, seminal vesicles, testes, thyroid gland, uterus, vagina.

Deviations from the current guideline: Relative to OECD 451 (2018), the number and sizing of groups, in addition to the dose levels and frequency was acceptable. However, the study omitted organ weights of the epididymides, thyroid (weighed post-fixation with parathyroids) and uterus. The minor deviations are not considered to affect the validity of this GLP and Guideline compliant study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

The increased absolute and relative ovary weights (+59% and +76%, respectively) in high dose females were attributed to grossly enlarged ovaries as a consequence of ovarian cysts (6/50 relative to 2/50 in controls). However, there were no treatment-related histopathological correlates and all pathological changes were considered to commonly occur in laboratory mice of the age and strain.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).

Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/effects observed).

Report:	[redacted] (1995) CGA17020 tech.: 18-month oncogenicity study in mice. [redacted]. Report 921063. Syngenta file: CGA17020/0336.

Guidelines: OECD 451 (1981)

GLP: Yes

Study design: Groups of fifty male and fifty female albino mice (ICO:CD1 Crl)) were administered dimethachlor by dietary inclusion at dose levels of 0, 20, 300 or 4000 ppm (equivalent to 0, 2.25, 32.3 and 488 mg/kg/day in males and 0, 2.17, 31.2 and 451 mg/kg/day in females) for a period of eighteen months. The test material was formulated at approximately 4-week intervals throughout the study and the control animals received untreated diet alone in the same way. Clinical signs, body weight and food intake were frequently monitored. Blood samples were taken for laboratory investigations at intervals during the study (Weeks 53 and 78). All designated animals were killed at the end of the scheduled interim and terminal treatment periods and any macroscopic changes noted. Specified organs were weighed, and selected tissues removed for histopathological examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations.
- Organ weights: adrenals, ovaries, testes.
- Histopathological examination: adrenal glands, epididymides, mammary area, ovaries, thyroid with parathyroid gland, pituitary gland, prostate gland, seminal vesicles, testes, uterus, vagina.

Deviations from the current guideline: Relative to OECD 451 (2018), the number and sizing of groups, in addition to the dose levels and frequency was acceptable. However, the study omitted organ weights of the epididymides, thyroid (weighed post-fixation with parathyroids) and uterus. The minor deviations are not considered to affect the validity of this GLP and Guideline compliant study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Lower mean adrenal weights were recorded for females treated at 4000 ppm. These were associated with lower terminal body weights in these animals, and no dose response was observed following adjustment of adrenal weights for body weights (Table 204). In addition these were not associated with histopathological findings and considered to be of no toxicological importance.

Table 204: Body weights, and absolute and relative relative adrenal weights in mice following 18 months of treatment with dimethachlor

Organ	**Dietary Concentration (ppm)**							
	Males				**Females**			
	0	**20**	**300**	**4000**	**0**	**20**	**300**	**4000**

Carcass weight (g)	53.92	53.42	54.59	48.67**	50.58	50.12	49.91	45.52**
adrenal absolute (mg)	6.915	6.317	7.147	6.984	17.58	19.78	16.72	14.60**
adrenal relative	0.139	0.127	0.142	0.154	0.374	0.422	0.363	0.339

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/effects observed).

Developmental studies in OECD Conceptual Framework level 4

Report:	[redacted]. (1994). Rat oral teratogenicity (gavage). Test No. 931108. [redacted]. Unpublished report. Syngenta file: CGA17020/0267

Guidelines: OECD 414 (1981)

GLP: Yes

Study design: Nulliparous female albino rats (Tif:RAIf SPF hybrids of RII/1 x RII/2, Sprague-Dawley derived) were mated with males of the same stock and proven fertility at an initial ratio of three females to one male. Groups of twenty-five of the resultant pregnant females were administered dimethachlor by daily oral gavage at dose levels of 0, 50, 350 or 700 mg/kg/day from Day 6 to Day 15 of gestation. The test material was formulated freshly each day and the control animals received the vehicle alone in the same way at the same dose volume of 10 mL/kg. Clinical signs, body weight and food intake of the parent females were frequently monitored during the gestation period. All dams were killed at the end of the treatment period (Day 21 of gestation) and any macroscopic changes noted with specific attention to the reproductive tract. The foetuses were removed by caesarean section and subject to detailed examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations of the dams with particular attention to the reproductive tract.
- Number of *corpora lutea* in each ovary.
- Weight of uterus and contents.
- Uterine contents: number and location of implantation sites (decedents) or live/dead foetuses early/late embryonic/foetal losses, and classification of uterine findings.
- Foetal necropsy: number and sex, weight, external examination, visceral examination, skeletal examination, and classification of foetal observations.

Deviations from the current guideline: The OECD 414 guideline was updated on 25 June 2018, to include measurement of maternal thyroid hormones (T4, T3 and TSH) and ano-genital distance (AGD) in rats, neither of which were considered in the current study. Furthermore, there were some deviations relative to the contemporaneous 2001 guideline, including the length of treatment, which considered the major period of organogenesis rather than the full length of gestation. The skeletons were also only singly stained with Alizarin red, rather than double stained with Alcian blue. Despite the lack of cartilage staining in this study, any significant changes would have been detected under light microscope.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

The test substance was toxic to dams at 350 and 700 mg/kg/day as indicated by the death of five females at 700 mg/kg/day and reduced weight gain and food intake at both dose levels. At these maternally toxic dose levels a slight foetal development delay was observed in the form of irregular ossification of the occipital bone, wide fontanel, poor and/or absent ossifications of phalanges.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/effects observed).

Report:	[redacted] (1993). Oral (gavage) teratogenicity study in rabbits. Test No. 921140. [redacted]. Unpublished report. Syngenta file: CGA17020/0216.

Guidelines: Equivalent to OECD 414 (2001)

GLP: Yes

Study design: Five groups of 20 sexually mature and inseminated rabbits (New Zealand White rabbits) were administered dimethachlor by daily oral gavage at dose levels of 0, 10, 100, 350 or 600 mg/kg/day from Day 6 to Day 18 of gestation. The female rabbits were fertilised by natural mating. The high dose group was terminated after two days of treatment due to severe maternal toxicity. The test material was formulated freshly each day and the control animals received the vehicle alone in the same way at the same dose volume of 10 mL/kg. Clinical signs, body weight and food intake of the parent females were frequently monitored during the gestation period. All dams were killed at the end of the treatment period (Day 28 of gestation) and any macroscopic changes noted with specific attention to the reproductive tract. The foetuses were removed by caesarean section and subject to detailed examination.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations of the dams with particular attention to the reproductive tract.
- Number of *corpora lutea* in each ovary.
- Weight of uterus and contents.
- Uterine contents: number and location of implantation sites (decedents) or live/dead foetuses early/late embryonic/foetal losses, and classification of uterine findings.
- Foetal necropsy: number and sex, weight, external examination, visceral examination, skeletal examination, and classification of foetal observations.

Deviations from the current guideline: The OECD 414 guideline was updated on 25 June 2018, to include measurement of maternal thyroid hormones (T4, T3 and TSH) and ano-genital distance (AGD) in rats, but remained unchanged for rabbits. However, there were some deviations relative to the contemporaneous 2001 guideline, including the length of treatment, which considered the major period of organogenesis rather than the full length of gestation. The skeletons were also only singly stained with Alizarin red, rather than double stained with Alcian blue. Despite the lack of cartilage staining in this study, any significant changes would have been detected under light microscope.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

The highest dose level in the study (600 mg/kg/day) proved too toxic to the dams and was terminated prior to the completion of gestation. Further mortality was recorded at dose levels of 350 and 100 mg/kg/day with body weight losses and reduced food intake also recorded for these animals during the gestation period. The slight reduction in the number of live foetuses at 350 and 100 mg/kg/day were considered related to the lower number of implantations in these groups and hence incidental to the treatment. There was no effect on the incidence and severity of foetal malformations in the external, visceral or skeletal examination.

CONCLUSIONS

Reliability score	**1** - Reliable without restriction
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/effects observed).

Report:	[redacted] (1994). Two-generation oral (dietary) reproduction toxicity study in the rat. Test No. 921141. [redacted]. Unpublished report. Syngenta file: CGA17020/0270.

Guidelines: OECD 416 (2001)

GLP: Yes

Study design: Five groups of twenty-five male and twenty-five female albino rats (Sprague-Dawley Crl:CD (SD)BR) were administered dimethachlor via the diet at inclusion levels of 0, 20, 300, 2000 and 4000 ppm from the start of treatment until necropsy (no data was presented on the calculated equivalent daily intakes of the test substance). Test formulations were prepared at monthly intervals throughout the treatment period. After 14 weeks of premating treatment, the parental (P) animals were mated for up to 21 days. The P females were allowed to litter and to rear their offspring (F1a generation) to weaning. After weaning of the F1a pups and review of the respective rearing and weaning data, a second mating of the P generation took place. Prior to the second mating, the P animals were maintained on treatment for a further 4 weeks. The P animals were then allowed to mate for maximally 21 days with a different partner from the same dose group to produce a second litter (F1b generation). Following an 18-week maturation period after weaning, the F1 parental animals (selected from the F1a offspring) were mated for up to 21 days. The F1 females were allowed to litter and to rear their offspring (F2a generation) to weaning. Additionally, F1 animals were selected from the F1b offspring and maintained until weaning of the F2a offspring. Clinical observations, body weight and food consumption were frequently monitored for all parental animals (P and F1) up to and including each mating, together with the recording of pregnancy and parturition data. For each generation detailed litter data was collated and specific developmental milestones evaluated.

Endpoints relevant for assessment of potential for endocrine disruption:

- Gross macroscopic observations
- Reproductive performance:
  - Pre-coital interval
  - Mating
  - Fertility
  - Duration of gestation
  - Parturition
  - Litter size (reductions in litter size can be indicative of abortions/resorptions/intra-uterine deaths)
- Offspring sex ratio, behavioural reflex, developmental landmarks and necropsy
- Organ weights: epididymides, testes (all animals of P and F1 generations).
- Histopathology: cervix, epididymides, ovaries, pituitary, prostate, seminal vesicles, testes, uterus, vagina (all animals of P and F1 generations).
- Foetal abnormalities relevant for assessment of potential for endocrine disruption.

Deviations from the current guideline: Relative to OECD 416 (2001), the number and sizing of groups, in addition to the dose levels and frequency was acceptable, and in accordance with OECD Guidance Document 106 (2009), the pituitary gland, prostate, seminal vesicle, ovary, uterus, cervix and vaginal tissues were evaluated histologically. However, oestrous cyclicity, quantitative ovarian follicle count, sperm parameters and sexual maturation were not specifically investigated.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

However, reduced pup weights were recorded from the 4000 ppm and 2000 ppm dose groups in the F1a, F1b and F2a generations. The reduced pup weights observed in both generations were associated with significant reductions in body weight gain and food intake of P and F1 animals at 4000 or 2000 ppm prior to mating and throughout gestation and lactation.

There was also an unusually high degree of pup loss in the F1a generation in all dose groups including the control. However, these findings were not replicated in the second mating of the P generation and therefore were considered incidental to treatment.

CONCLUSIONS

Reliability score	**1** - Reliable without restrictions
Relevance score	**Medium** (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Indicative for evidence of effects relevant for the assessment of endocrine disruption** (indicative study/effects observed).

IN VIVO DATA – NON-MAMMALIAN SPECIES

Existing Data in OECD Conceptual Framework level 1

The following studies conducted as part of the regulatory data package for registration of dimethachlor were not specifically designed for detection of endocrine disrupting properties, but as they cover life stages and endpoints relevant to growth (fish study) and reproduction (bird study), they have been included in the current evaluation.

Report:	[redacted] (1993). Report on the prolonged toxicity test of CGA 17020 T to rainbow trout. Test No. 928365. [redacted]. Unpublished report. (Syngenta file no: CGA17020/0209)

Guidelines: OECD Guideline 204: Fish prolonged toxicity test (1984)

GLP: Yes

Study design: Rainbow trout were exposed to five mean measured concentrations of dimethachlor (0.0036, 0.014, 0.058, 0.21 and 0.85 mg/L) and a dilution water control, under flow-through conditions. One aquarium containing 10 fish was assigned to each treatment and control. Fish were exposed for 21 days. Mortality and clinical signs were evaluated daily except Sunday and the body weight and length were measured at the start and end of exposure.

Endpoints relevant for assessment of potential for endocrine disruption

- Body weight and length
- Clinical signs

Effects on endpoints relevant for assessment of potential for endocrine disruption

None.

CONCLUSIONS

Reliability score	**1** – Reliable without restrictions
Relevance score	**Medium** – Endpoint(s) in a multi-generation test or other repeat dose standard toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity
Overall significance	**Low**

Report:	[redacted], and [redacted], (2018), Dimethachlor - Toxicity to Zebrafish (*Danio rerio*) in an Early-Life Stage Test. Report Number 125391232. [redacted]. (Syngenta file no CGA017020_10280)

Guidelines: OECD Guideline 210: Fish, Early-Life Stage Toxicity Test (2013)

GLP: Yes

Study design: Newly fertilised *Danio rerio* eggs (25 per replicate, four replicates) were exposed under flow-through conditions to dimethachlor technical at nominal concentrations of 0.03, 0.1, 0.3, 1 and 3 mg a.s/L (mean measured concentration ranged from 95 – 115 % of the nominal) and the reconstituted water control. Embryos were exposed for 30 days after hatching (day 4 after insertion of eggs was designated as day 0 of the 30 day post-hatch period). Effects on hatching success, post-hatch survival, and larval growth (weight and length) were recorded.

Endpoints relevant for assessment of potential for endocrine disruption

- Hatching success
- Larval growth (length and weight)

Effects on endpoints relevant for assessment of potential for endocrine disruption

None.

The effect on post-hatch survival (significant at the top test concentration of 3 mg/L) should be interpreted as systemic toxicity as no effects on endpoints potentially sensitive to endocrine disrupters (hatching, larval growth) were observed in the study.

CONCLUSIONS

Reliability score	**1** – Reliable without restrictions
Relevance score	**Medium** (Endpoint(s) in a multi-generation test or other repeat dose standard toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity).
Overall significance	**Low**

Short term non-mammalian studies in OECD Conceptual Framework level 3

None available.

Non-mammalian studies in OECD Level 4

Report:	[redacted]. (1995). CGA 17020: Japanese quail – Dietary reproduction and tolerance studies. Report No. CBG 643/942969. [redacted], UK. Unpublished report. (Syngenta file no: CGA17020/0295)

Guidelines: OECD Guideline 206: Avian Reproduction Test (1984)

GLP: Yes

Study design: Twenty replicates (one male and one female per replicate) were exposed to dietary concentrations of dimethachlor (100, 300 and 900 ppm) and a control. Birds were exposed for 10 weeks prior to egg laying and 8 weeks during egg collection. Adult mortality, symptoms of toxicity, body weight, feed consumption, gross pathology, eggs laid, eggs cracked, viable embryos, eggshell thickness, and number and body weight of hatchlings and 14-day old survivors were assessed.

Endpoints relevant for assessment of potential for endocrine disruption

- Egg production, egg shell thickness, egg quality
- Viability of embryos
- Hatchability, number and weight of hatchlings
- Gross pathology

Effects on endpoints relevant for assessment of potential for endocrine disruption

- Reduced initial body weight of hatchlings in all treated groups

Initial body weight of hatchlings was significantly reduced in all treated groups compared to control. This is considered not to be of importance, as there was no effect observed on 14-day hatchling body weight, and there was no consistent concentration-response relationship.

Adult food consumption over the treatment period was significantly reduced in 900 ppm, but no effects on adult body weight were observed. The effect on food consumption on its own is not considered to be relevant for the assessment of potential for endocrine disruption.

CONCLUSIONS

Reliability score	**2** – Reliable with restrictions (test concentrations confirmed in preliminary study, but not in main study).
Relevance score	**Medium** (Endpoint(s) in a multi-generation test or other repeat dose standard toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity)
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (indicative study/no effects observed)

Non-mammalian studies in OECD Level 5

None available.

INTEGRATION AND ASSESSMENT OF LINES OF EVIDENCE

LINES OF EVIDENCE FOR ENDOCRINE DISRUPTING POTENTIAL RELEVANT TO HUMANS

Dimethachlor has been extensively tested in mammalian species, including multiple studies in Levels 4 and 5 of the OECD Conceptual Framework. Evaluation of the database indicates that administration of dimethachlor does not result in adverse effects in '*EATS-mediated parameters'*.

Tables integrating an assembling the lines of evidence on the basis of adversity in parameters considered '*EATS-mediated*' or '*sensitive to, but not diagnostic of EATS'* in accordance with EAS and T modalities are provided below.

Table 205: Integrating and assembling the lines of evidence for thyroid disruption in mammals

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
Integrated line of evidence for endocrine activity	None available									
Integrated lines of evidence for adversity	**EATS-mediated parameters**	Thyroid (histopathology)	Dog	4	Oral	4000 ppm	No effect; highest dose 4000 ppm	No effect on thyroid histopathology	No effect on thyroid adversity *in vivo*. There was no treatment related effect on thyroid parameters (weight and histology) in any of the species at any of the dose levels tested. Treatment led to significant decreases in bodyweight and increased liver weight, with corroborative histological findings (hepatocyte hypertrophy).	Thyroid
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	3000 ppm	No effect; highest dose 3000 ppm			
			Mouse	4	Oral	7000 ppm	No effect; highest dose 7000 ppm			
			Mouse	13	Oral	7000 ppm	No effect; highest dose 7000 ppm			
			Mouse	80	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Mouse	80	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	4	Oral	5000 ppm	No effect; highest dose 5000 ppm			
			Rat	4	Dermal	1000 mg/kg/day	No effect; highest dose 1000 mg/kg/day			
			Rat	13	Oral	6000 ppm	No effect; highest dose 6000 ppm			
			Rat	52	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	104	Oral	4000 ppm	No effect; highest dose 4000 ppm			
		Thyroid (organ weight)	Dog	4	Oral	4000 ppm	No effect; highest dose 4000 ppm	No evidence of a consistent effect on thyroid weight in any of the species at any of the doses tested. Slight increase in		
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	3000 ppm	No effect; highest dose 3000 ppm			
			Mouse	13	Oral	7000 ppm	Slight increase in thyroid weight in all			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
							dose groups. Not associated with treatment.	relative thyroid weight observed in F1 males was considered spontaneous and not related to treatment.		
			Rat	13	Oral	6000 ppm	No effect; highest dose 6000 ppm			
	Parameter sensitive to, but not diagnostic of EATS	Pituitary (histopathology)	Dog	4	Oral	4000 ppm	No treatment related effect. However, increase in developmental cysts in top dose males.	No evidence of effects on the pituitary in any species at any of the doses tested		
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	3000 ppm	No effect; highest dose 3000 ppm			
			Mouse	4	Oral	7000 ppm	No effect; highest dose 7000 ppm			
			Mouse	80	Oral	4000 ppm	No effect; highest dose 4000 pppm			
			Mouse	80	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	4	Oral	5000 ppm	No effect; highest dose 5000 ppm			
			Rat	13	Oral	6000 ppm	No effect; highest dose 6000 ppm			
			Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	52	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	104	Oral	4000 ppm	No effect; highest dose 4000 ppm			
Evidence of general toxicity		Bodyweight	Dog	4	Oral	4000 ppm	Decreases in bodyweight in males ande females (2-3%)	Consistent statistically significant dose-dependent effects on		N/A
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
			Dog	13	Oral	3000 ppm	Bodyweight loss in males and reduced bodyweight gain in both sexes (-164% males; >-12% females)	bodyweight and bodyweight gain in rats, mice and dogs		
			Mouse	4	Oral	7000 ppm	Marked reductions in bodyweight gain in males (-37% controls)			
			Mouse	13	Oral	7000 ppm	Reductions in bodyweight gain in males (-20% controls)			
			Mouse	80	Oral	4000 ppm	Reduced bodyweight from at week 77 (-18% males; -19% females)			
			Mouse	80	Oral	1500 ppm	Dose dependent decrease in bodyweight in males.			
			Rat	4	Oral	750/350 mg/kg/day	Bodyweight loss (-4.6%) and marked reductions in bodyweight gain in males (-22%)			
			Rat	4	Oral	3000 ppm	Dose dependent reduction in cumulative bodyweight gain (-7 to -17% in males; -9 to -11 in females)			
			Rat	4	Dermal	1000 mg/kg/day	No effect at limit dose			
			Rat	13	Oral	6000 ppm	Reduced group mean bodyweight gain (-18% males; -10% females)			
			Rat	2-Gen	Oral	4000 ppm	Reduction in parental pre-mating body weight (-9% males; -11% females). There			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
							was no effect during gestation or lactation.			
			Rat	52	Oral	4000 ppm	Reduced bodyweight gain (-7.6% males; -9.6% females)			
			Rat	104	Oral	4000 ppm	Reduced bodyweight gain (-11% males; -15% females)			
		Liver weight (relative)	Dog	4	Oral	2000 ppm	>20% increase in males and females	Liver is the target organ for the compound. Consistent statistically significant dose dependent effects on liver weight with corroborative hepatocyte hypertrophy.		
			Dog	13	Oral	1250 ppm	No effect in relative weight. However slight increase in absolute liver weight at 1250 ppm in females			
			Dog	13	Oral	300 ppm	>17% increase in females and males at 1000 ppm			
			Mouse	4	Oral	1000 ppm	>13% increase in males and females at 3000 ppm			
			Mouse	13	Oral	1000 ppm	>10% increase in males and females at 3500 ppm			
			Mouse	80	Oral	4000 ppm	>12% increase in males and females			
			Mouse	80	Oral	1500 ppm	>11% dose-dependent increase in males and females on weeks 79-81.			
			Rat	4	Oral	3000 ppm	>13% increase in males and females.			
			Rat	4	Oral	750/350 mg/kg/day	>20% increase in males and females			
			Rat	4	Dermal	1000 mg/kg/day	No effect at limit dose			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
			Rat	13	Oral	6000 ppm	>13% dose dependent increase in males and females			
			Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	52	Oral	4000 ppm	20% increase in females			
			Rat	104	Oral	4000 ppm	9% increase in males; no effect in females			
		Liver (histopathology)	Dog	4	Oral	2000 ppm	Hepatocellular hypertrophy in mals and females at 4000 ppm			N/A
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	1000 ppm	Minimal to moderate centrilobular hepatocellular hypertrophy in males and females.			
			Mouse	4	Oral	3000 ppm	Slight centrilobular hepatocellular hypertrophy in males and females			
			Mouse	13	Oral	1000 ppm	Hepatocyte hypertrophy in males and females at 3500 ppm			
			Mouse	80	Oral	4000 ppm	Moderate hepatocyte hypertrophy in males and females			
			Mouse	80	Oral	1500 ppm	Hepatocellular hypertrophy in males and females			
			Rat	4	Oral	3000 ppm	Slight hepatocellular hypertrophy in males and females			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
			Rat	4	Oral	750/350 mg/kg/day	Minimal to moderate hepatocellular hypertrophy in males and females			
			Rat	4	Dermal	1000 mg/kg/day	No effect at limit dose			
			Rat	13	Oral	6000 ppm	Minimal hepatocellular hypertrophy in males and females			
			Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	52	Oral	4000 ppm	Cytoplasmic inclusion bodies and enlargement of periportal hepatocytes in males. Hepatocyte hypertrophy in males and females			
			Rat	104	Oral	4000 ppm				

LINES OF EVIDENCE FOR ENDOCRINE DISRUPTING POTENTIAL RELEVANT TO NON-TARGET ORGANISMS

Lines of evidence for adversity

According to the Criteria an adverse effect relevant to non-target organisms *"is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences"*

Effect on endpoints relevant to survival, growth, development and reproduction in available ecotoxicology studies may therefore be regarded as relevant to establishing evidence for adverse effects. However, as indicated in the Guidance document with respect to validated test guidelines informative for endocrine disrupting properties, such endpoints can only be considered '*Sensitive to, but not diagnostic of, EATS'*.

Survival
An avian reproduction study (OECD 206) in Japanese quail is available for dimethachlor ([redacted] 1995). The study reported no effects on parental mortality at any dose.

A prolonged toxicity test in rainbow trout (OECD 204) is available for dimethachlor ([redacted] 1993). No effects on mortality were observed.

A fish early life stage study (OECD 210) in zebra fish is available for dimethachlor ([redacted] and [redacted] 2018) that reported significant reduction in survival at the top test concentration of 3 mg a.s./L. This indicates that the upper end of the test concentration range was above the MTC.

Growth
Hatchling body weight is the apical endpoint relevant to growth in avian reproduction studies (OECD 206 and similar). In the study on effects of dimethachlor in Japanese quail ([redacted] 1995), there was a significant reduction in initial hatchling bodyweight at all test concentrations. There was no treatment-related trend evident, and no effects were observed on 14-day hatchling body weight.

Length and wet/dry weight are the apical endpoints relevant to growth in the fish early life-stage test (OECD 210) and the prolonged toxicity test (OECD 204). In both available studies no effects were reported on fish length and weight.

The effect on growth reported in birds only relates to initial hatchling body weight, in a study not specifically designed for identification of endocrine disrupting properties. Moreover, the growth endpoints in this test guideline are indicators of toxicity through other non-endocrine modes of action, as acknowledged by the classification of such endpoints in the Appendix E spreadsheet as 'Sensitive to but not diagnostic of'. This study therefore provides no evidence of effects of dimethachlor in birds through endocrine disruption.

Development
Hatchability is the apical endpoint relevant to development in the avian reproduction test (OECD 206), though this endpoint also integrates embryonic survival. Neither embryonic survival nor hatchability were reduced at any test concentration in the reproduction study in Japanese quail.

Hatching success is the apical endpoint relevant to development in the fish early life-stage test (OECD 210). In the study in the zebra fish hatching success was not reduced at any test concentration.

The prolonged fish toxicity test (OECD 204) does not cover the relevant life stage to be informative on development.

The available studies in fish and birds therefore provide no evidence of effects of dimethachlor on development through endocrine disruption or any other mechanism.

Reproduction
Apical endpoints relevant to reproduction in the avian studies include egg production, egg viability, egg quality (size, cracking), and gross pathology. In the study in the Japanese quail there were no effects of dimethachlor on any reproductive parameters.

The prolonged toxicity test and the early life stage study in fish (OECD 204, OECD 210) do not cover the relevant life stage to be informative on reproduction.

The available ecotoxicology studies therefore provide no evidence of effects of dimethachlor on reproduction through endocrine disruption or any other mechanism.

Table 206: Integrated and assembled lines of evidence for non-target organisms

	Grouping	Line(s) of Evidence	Species	Exposure	Route of exposure	Effect Concentration	Observed effects	Assessment	Assessment of integrated line of evidence	Modality
Integrated line of evidence for endocrine activity	None available									
Integrated line of evidence for adversity	**EATS-mediated parameters**	None available								
	Sensitive-to-but not diagnostic of EATS	Growth	Japanese quail	20 weeks	Diet	100 ppm	Reduced initial hatchling bodyweight	Not indicative of endocrine disruption – no treatment-related trend and no effect on 14-day bodyweight	No evidence for endocrine mediated adverse effects	
Evidence of general toxicity	Mortality		*Danio rerio*	30 d	Water	3 mg/L	Mortality	Not indicative of endocrine disruption – no effects on endpoints other than mortality	Sufficient evidence of systemic toxicity to exclude endocrine mechanism as plausible mode of action - absence of other effects potentially indicative of endocrine disrupting properties	

Lines of evidence for EATS-related endocrine activity
No *in vivo* mechanistic studies in non-target organisms are available for dimethachlor

INITIAL ANALYSIS OF THE EVIDENCE

ANALYSIS OF EVIDENCE RELATED TO ED POTENTIAL FOR HUMANS
A number of potential scenarios are described in Section 3.4.4 and Table 5 of the EFSA-ECHA Guidance Document (EFSA-ECHA 2018). In order to determine which scenario is most applicable to the data set it is necessary to assess both the sufficiency of the assessment of endocrine related adversity and the available data on endocrine related adversity.

Data set sufficiency in mammals
A dataset is considered to have sufficiently investigated EAS related adversity in relation to mammals if the parameters investigated in a two-generation reproductive toxicity study (OECD TG 416) implicit to the 2001 revision of this guideline have been assessed (EFSA-ECHA 2018). The dimethachlor two-generation toxicity study does not consider all parameters required for compliance to the current guideline (Table 207). In accordance with the EFSA-ECHA (2018) Guidance, EAS related adversity has not been sufficiently investigated and further *in vitro* and *in vivo* mechanistic data is triggered.

Table 207: Comparison of the parameters sensitive to perturbation of the endocrine system required in the 2001 revision of OECD 416 and the two-generation toxicity study with dimethachlor

Parameter	**Assessed in the two-generation study with dimethachlor**
Gross necropsy (macroscopic) observations	Yes
Reproductive performance: • Pre-coital interval • Mating (copulation indices) • Fertility • Gestation index • Duration of gestation • Parturition • Litter size (reductions in litter size can be indicative of abortions/resorptions/intra-uterine deaths) • Number of implantations	Yes
Number of *corpora lutea*	Yes
Sex ratio	Yes
Oestrus cyclicity	No
Sexual maturation (vaginal opening and preputial separation)	No
Ano-genital distance	No
Sperm analysis (number, motility and morphology)	No
Organ weights: uterus, ovaries, testes, epididymides, prostate, seminal vesicles with coagulating glands, pituitary, thyroid and adrenal glands	No
Histopathological examination: vagina, uterus (with cervix), ovaries, testis, epididymis, seminal vesicles, prostate (and coagulating gland)	Yes

A dataset is considered to have sufficiently investigated thyroid related adversity in relation to mammals if the parameters investigated in OECD TG 407, 408, 409 (and/or the one-year dog study, if available), 416 and 453 have been assessed. Assessment of the potential for dimethachlor to alter thyroid related parameters (histology and/or weight) has been conducted in studies spanning a range of durations (from 28-days to 104-weeks), in the mouse, rat and dog, and through multiple exposure routes (see data reviews in Section 4). It is therefore determined that the potential for thyroid related effects in relation to mammals has been sufficiently addressed and that no further data is required to determine that there is no concern for thyroid adversity in the mammalian toxicity database for dimethachlor.

Analysis of endocrine related adversity in mammals
No endocrine related adversity has been reported in an array of species administered dimethachlor. However, whilst the dimethachlor data set includes a sufficient assessment of thyroid related adversity, EAS related adversity was not sufficiently evaluated in accordance with the EFSA-ECHA Guidance Document (Scenario 2a(iii)), and *in vitro* and *in vivo* data generation to ameliorate concerns pertaining to EAS activity is triggered.

ANALYSIS OF EVIDENCE RELEVANT TO ED POTENTIAL IN NON-TARGET ORGANISMS
Studies recommended in the guidance document as sufficient for investigation of 'EATS-mediated adversity' in non-target organism are as follows:

- fish full life study (MEOGRTS, OECD 240, or equivalent)
- Larval amphibian growth and development assay (LAGDA, OECD 241), though a negative AMA is acceptable in lieu of a LAGDA

EAS modality
A fish full life cycle test is not available for dimethachlor. In assembling the lines of evidence for adversity in non-target organisms in the preceding section, it is clear that there is no evidence of EAS-mediated adversity in the available ecotoxicology studies. Parameters relevant to survival and growth in the fish early life stage toxicity and bird reproduction study may be considered 'sensitive to, but not diagnostic of, EATS', and were indicative of systemic toxicity. There were no effects indicative of effects on the reproductive system. With reference to the assessment strategy set out in Figure 1 of the ECHA-EFSA Guidance (Figure 2.3.1-1 in this document), Scenario 2b is not relevant in the present evaluation.

As noted in Section 5, endocrine activity has not been observed in non-target organisms with respect to the EAS modalities. With reference to Figure 2.3.1-1, Scenario 2a(i) is not relevant in the present evaluation.

The Guidance states in Section 3.4.2. that 'to consider the EAS modalities for non-target organisms sufficiently investigated, preferably the fish short-term reproduction assay (FSTRA; OECD 229) should have been conducted. As no such test is available for dimethachlor, Scenario 2a(iii) is relevant – gather more information on endocrine activity in EAS modalities.
Considering the purpose of conducting a Level 3 fish study with dimethachlor – to investigate EAS activity (not adversity) - Syngenta propose to conduct this study according to OECD TG 230, the 21-day fish screening assay, which is also considered acceptable in the ECHA-EFSA guidance (section 3.4.2).

T modality
A LAGDA (OECD 241) is not available for dimethachlor, nor is an AMA (OECD 231).

Consequently, with reference to Figure 1 in the Guidance document (presented as Figure 2.3.1-1 in this document), it is not possible to conclude from the available ecotoxicology dataset that dimethachlor does not meet the ED criteria (Scenario 1a), with respect to the T modality.

In assembling the lines of evidence for adversity in non-target organisms in the preceding section, it is clear that there is no evidence of T-mediated adversity in the available ecotoxicology studies.

- No T-relevant adverse effects were reported in the two avian reproduction studies
- Parameters relevant to survival, growth, development in the fish ELS study may be considered 'sensitive to, but not diagnostic of, EATS' and were only affected at higher test concentrations in the context of systemic/overt toxicity

Therefore, Scenario 2b is not relevant to the present evaluation: T-mediated adversity has not been observed. Moreover, no T-mediated adversity is evident from the more comprehensive set of mammalian studies. There were no effects on thyroid histopathology (i.e. follicular hypertrophy or hyperplasia) at any test concentrations, and no treatment-related effect on thyroid weight, in any of the model species.

With regard to endocrine activity, as noted above, no AMA is available for dimethachlor, nor is *in vitro* data in OECD CF Level 2. Consequently, activity of dimethachlor with respect to key targets in the hypothalamic-pituitary-thyroid axis, namely thyroid peroxidase (TPO), Sodium/Iodide Symporter (NIS) and deiodinase enzymes (I,II and III) is currently unknown. Endocrine activity has therefore not been sufficiently investigated with respect to the T modality and Scenario 2a(iii) is relevant – gather more information (on endocrine activity).

MOA ANALYSIS

MOA Analysis – Human Health
Not relevant at present time. No effect on any parameter described as "*EATS-mediated*" in the guidance document was identified in the dimethachlor toxicology database.

MOA Analysis – Non-target organisms

Not relevant at present time for EAS modalities - no effects on any parameter described as "*EAS-mediated*" in the guidance document were identified in the dimethachlor ecotoxicology database.

CONCLUSIONS

HUMAN HEALTH

The available data on dimethachlor do not indicate effects consistent with endocrine disruption. Thyroid parameters have been sufficiently investigated and the ED criteria are not met for the T modality. However, in accordance with the EFSA-ECHA (2018) Guidance, EAS-mediated parameters have not been sufficiently investigated *in vivo*. Applying this Guidance Document, *in vitro* and *in vivo* mechanistic studies are triggered to further investigate EAS modalities in the absence of a modern two-generation study.

In accordance with the EFSA-ECHA (2018) Guidance, the following *in vitro* and *in vivo* mechanistic studies are triggered for EAS modalities:

1) *In vitro* steroidogenesis assay (OECD 456)
2) *In vitro* ER transactivation assay (OECD 455)
3) *In vitro* AR transactivation assay (OECD 458)
4) Uterotrophic assay (OECD 440)
5) Hershberger assay (OECD 441)

NON-TARGET ORGANISMS

Available ecotoxicology data do not indicate effects consistent with endocrine disruption, however, considering the available data in accordance with the EFSA-ECHA Guidance document (2018), there is not currently a fully adequate dataset to conclude on whether dimethachlor exhibits endocrine disrupting properties in non-target organisms according to the Endocrine Disruption Criteria (2018/605).

There are no ecotoxicology tests available for dimethachlor that are directly informative on the thyroid modality, there is no indication of thyroid adversity in the mammalian database. In the interests of minimising animal use, congruent with the Regulation (EC) 1007/2009, the applicant proposes to further investigate potential for T-mediated endocrine activity of dimethachlor in available *in vitro* assays.

To make sufficient data available to reach a conclusion, it was agreed with the applicant to conduct the following studies:

In vivo mechanistic studies (EAS modality)

- 21-day fish screening assay (OECD 230) in the Fathead minnow.

In vivo mechanistic assays to assess T activity against

- Amphibian Metamorphosis Assay (OECD 231)

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RMS assessment

ED assessment for humans

ED assessment for dimethachlor is based on regulatory mammalian toxicology studies for dimethachlor, namely sub-acute, sub-chronic, chronic, developmental and reproductive toxicity studies in rats, mice, dogs and rabbits. In silico, in vitro or in vivo mechanistic data (OECD Conceptual Framework Level 1, 2 and 3) were not identified for dimethachlor.

Within OECD Conceptual Framework level 4, the Applicant included all available short-term and long term toxicity studies, as well as developmental studies, previously described in the RAR:

- [redacted] (1992a). 4-week oral toxicity (feeding) study in the rat. Test No. 921024. [redacted]. Unpublished report. Syngenta file: CGA17020/0179
- [redacted] (1993). 28-day oral cumulative toxicity study in rats (gavage). Test No. 921091. [redacted]. Unpublished report. Syngenta File: CGA17020/0207
- [redacted] (1992b). 4-week oral toxicity (feeding) study in the mouse. Test No. 921032. [redacted]. Unpublished report. Syngenta file: CGA17020/0178

- [redacted] (1994). 3-month oral toxicity study in rats (dietary). Test No. 931117. [redacted]. Unpublished report. Syngenta file: CGA17020/0265
- [redacted] (1999). 3-month range-finding oral toxicity study in mice (dietary). Test No. 981115. [redacted]. Unpublished report. Syngenta file: CGA17020/0505
- [redacted] (1993). 28-day range finding toxicity study in beagle dogs. Test No. 921193. [redacted]. Unpublished report. Syngenta file: CGA17020/0220
- [redacted] (1994). 3-month dietary toxicity study in beagle dogs. Test No. 921194. [redacted]. Unpublished report. Syngenta file: CGA17020/0266
- [redacted]. (1974). 90-Day dietary toxicity study in dogs. Test No. [redacted]. [redacted]. Unpublished report. Syngenta file: CGA17020/0112
- [redacted] (1993d). 28-day repeated dose dermal toxicity study in the rat. Test No. 921090. [redacted]. Unpublished report. Syngenta file: CGA1702/0208.
- [redacted]nth carcinogenicity and chronic toxicity study in rats (dietary). Test No. 921064. [redacted]. Unpublished report. Syngenta file: CGA17020/0301
- [redacted] (2001). 18-month oncogenicity study in mice (dietary). Test No. 991036. [redacted]. Unpublished report. Syngenta file: CGA17020/0583
- [redacted] (1995) CGA17020 tech.: 18-month oncogenicity study in mice. [redacted]. Report 921063. Syngenta file: CGA17020/0336
- [redacted]. (1994). Rat oral teratogenicity (gavage). Test No. 931108. [redacted]. Unpublished report. Syngenta file: CGA17020/0267
- [redacted] (1993). Oral (gavage) teratogenicity study in rabbits. Test No. 921140. [redacted]. Unpublished report. Syngenta file: CGA17020/0216

Within OECD Conceptual Framework level 5 only one study was available:

- [redacted] (1994). Two-generation oral (dietary) reproduction toxicity study in the rat. Test No. 921141. [redacted]. Unpublished report. Syngenta file: CGA17020/0270.

The following findings were described in these studies.

Testis

Testicular changes were noted in rats and dogs, but they are not considered to be treatment-related and/or toxicologically relevant.

Increased testes weights relative to body weight were observed in high-dose rats in 3-month oral study ([redacted], 1994). However, the absolute testes weights were similar to controls, and this change is considered to be secondary to reduced body weight in high-dose males. Decreased absolute testes weight was reported in low dose males in 28-day dermal study in the rat ([redacted], 1993d). In the absence of a dose-response relationship this change was not considered treatment-related.

Tubular degeneration/atrophy was noted in 28-day oral study in rats ([redacted], 1993). However, the effect is considered to be the result of severe systemic toxicity since it was described only in the top-dose males in which marked systemic toxicity, including mortality, was observed. Males that survived to scheduled termination (with dose reduction from 750 to 350 mg/kg bw/day) did not present any testicular changes. In 3-month oral study in rats ([redacted], 1994), testicular tubular atrophy was also observed, but it did not follow dose-response pattern (the incidence was 1, 1, 0, 1 across 0, 30, 1000 or 6000 ppm groups, respectively). In 24-month carcinogenicity and chronic toxicity study in rats ([redacted] and [redacted], 1995), an increased incidence of the fluid content of the testicular tunica albuginea and testicular tubular atrophy was noted in top-dose males. Nevertheless, these findings are considered to represent spontaneous and age-related changes. Higher incidence is considered to be a consequence of higher survival of the top-dose group in comparison to control or other dose groups.

In dogs, the minimal focal tubular atrophy in the testis was observed in 1/2 males of top-dose group in 28-day range finding study ([redacted], 1993), but it is considered incidental. Although the incidence was above historical control range provided by the Applicant (0%), only 8 dogs were included in historical controls, and this finding is known

to occur spontaneously at high rate in young Beagle dogs (under 1 year of age). Additionally, no toxicologically relevant testicular effects were seen in 3-month dog study ([redacted], 1994). In [redacted] (1994) study, namely, testicular tubular atrophy was found in one of the two males of the low-dose group, so it lacked dose dependency.

Ovary

Increased ovarian weights (absolute and/or relative) were noted for rats, mice and dogs, but in the absence of dose response and/or histopathological correlate, they were not considered treatment-related or toxicologically relevant.

In 28-day dermal toxicity study in the rat ([redacted], 1993d), an increase in absolute ovary weights in females at the lowest (+30%) and highest (+29%) dose groups was reported. In the absence of a clear dose-response relationship these changes are not considered treatment-related.

In 18-month oncogenicity study in mice ([redacted], 2001), the increased absolute and relative ovary weights in high dose females were attributed to grossly enlarged ovaries as a consequence of ovarian cysts. However, there were no treatment-related histopathological correlates (ovarian cysts were not considered treatment-related) and all pathological changes were considered to commonly occur in laboratory mice of the age and strain.

In 28-day range finding toxicity study in beagle dogs ([redacted], 1993), increases in absolute ovary weight were noted at the mid-dose group, in addition to increased relative ovary weights at the mid (+35%) and high (+33%) dose groups. These findings were not observed in the subsequent 90-day study, and in the absence of a histopathological correlate, were not considered related to dimethachlor treatment.

Uterus

Uterine atrophy was noted in one female at the high dose (3000 mg/kg bw/day) in 3-month dietary toxicity study in beagle dogs ([redacted], 1994). The RMS disagrees with the Applicant that this change is a high-dose effect, since the female in which uterine atrophy was observed had a similar body weight increase as control females and did not show clinical signs of toxicity. Nevertheless, since uterine atrophy was not observed in other studies, the RMS does not consider that this isolated case (one animal in a single experiment) indicates endocrine disrupting property of dimethachlor.

The RMS notes that dilation of uterine horns and thickening of the cervix were found in single females of all groups in 28-day study in the mouse ([redacted], 1992b), but that these changes are considered to represent oestrous cycle changes rather than pathological alterations.

Thyroid

Increased thyroid weights or enlarged thyroids were observed in mice, but these changes are not considered to be treatment-related and/or toxicologically relevant.

A slight increase in thyroid weights (absolute and relative to body weight) was reported in females treated with 1000, 3500 or 7000 ppm (+15.0%, +18.7% and +16.3% relative to body weight, respectively) in 3-month range-finding oral toxicity study in mice ([redacted], 1999). In the absence of a dose-response relationship, statistical significance and a histopathological correlate, the increase in thyroid weights were not considered toxicologically relevant.

The RMS notes that an increased number of enlarged thyroids was noted at necropsy in mid-high and high dose females (≥ 1500 ppm) in 18-month oncogenicity study in mice ([redacted], 2001) (thyroids were not weighed in the study). However, in the absence of corroborative histopathological findings and clear dose-response pattern (the incidences were 1, 6, 2, 9, 9 at 0, 20, 300, 1500, and 4000 ppm, respectively), the RMS considers that this change is not toxicologically relevant.

Parathyroid

An increased number of developmental cysts in the parathyroid gland were noted in high dose males in 28-day range finding toxicity study in dogs ([redacted], 1993). However, this is a common occurrence in this strain of Beagle dogs, and due to the developmental nature of the lesion, it cannot be attributed to dimethachlor treatment.

Adrenals

An increase in absolute and relative adrenal weight was reported in low dose males in 28-day dermal toxicity study in the rat ([redacted], 1993d). Since there was no dose-response pattern, the change is not considered treatment-related.

In 24-month carcinogenicity and chronic toxicity study in rats ([redacted] and [redacted], 1995), a decrease in absolute adrenal weights for mid and high-dose females was observed. However, these values were within historical control range and in the absence of a histopathological correlate were not considered toxicologically relevant. Also, in 18-month oncogenicity study in mice ([redacted], 1995), lower mean adrenal weights were recorded in top-dose

females. Since this change was associated with lower terminal body weights in these animals, no dose-response was observed following adjustment of adrenal weights for body weights, and no histopathological correlates were found, it is not considered relevant.

An increased incidence of fatty change in the adrenal cortex was reported in mid-dose males in 3-month oral toxicity study in rats (, 1994). In the absence of a dose-response, the finding is not considered treatment related.

Reproductive toxicity parameters

Reduced pup weights in two-generation reproduction toxicity study in the (, 1994) and a slight foetal development delay in oral teratogenicity study in rat 994) were observed at maternally toxic doses. These changes are, therefore, not considered indicative of endocrine disrupting property. It should be noted, however, that oestrous cyclicity, quantitative ovarian follicle count, sperm parameters and sexual maturation were not specifically investigated for dimethachlor.

Table 208: The lines of evidence for thyroid modality in mammals

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
Integrated line of evidence for endocrine activity	None available									
Integrated lines of evidence for adversity	**EATS-mediated parameters**	Thyroid (histopathology)	Dog	4	Oral	4000 ppm	No effect; highest dose 4000 ppm	No effect on thyroid histopathology	No effect on thyroid adversity*in vivo*. There was no treatment related effect on thyroid parameters (weight and histology) in any of the species at any of the dose levels tested. Treatment led to significant decreases in bodyweight and increased liver weight, with corroborative histological findings (hepatocyte hypertrophy).	Thyroid
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	3000 ppm	No effect; highest dose 3000 ppm			
			Mouse	4	Oral	7000 ppm	No effect; highest dose 7000 ppm			
			Mouse	13	Oral	7000 ppm	No effect; highest dose 7000 ppm			
			Mouse	80	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Mouse	80	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	4	Oral	5000 ppm	No effect; highest dose 5000 ppm			
			Rat	4	Dermal	1000 mg/kg/day	No effect; highest dose 1000 mg/kg/day			
			Rat	13	Oral	6000 ppm	No effect; highest dose 6000 ppm			
			Rat	52	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	104	Oral	4000 ppm	No effect; highest dose 4000 ppm			
		Thyroid (organ weight)	Dog	4	Oral	4000 ppm	No effect; highest dose 4000 ppm	No evidence of a consistent effect on thyroid weight in any of the species at any of the doses tested. Slight increase in relative thyroid		
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	3000 ppm	No effect; highest dose 3000 ppm			
			Mouse	13	Oral	7000 ppm	Slight increase in thyroid weight in all dose groups. Not			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
							associated with treatment.	weight observed in F1 males was considered spontaneous and not related to treatment.		
			Rat	13	Oral	6000 ppm	No effect; highest dose 6000 ppm			
	Parameter sensitive to, but not diagnostic of EATS	Pituitary (histopathology)	Dog	4	Oral	4000 ppm	No treatment related effect. However, increase in developmental cysts in top dose males.	No evidence of effects on the pituitary in any species at any of the doses tested		
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	3000 ppm	No effect; highest dose 3000 ppm			
			Mouse	4	Oral	7000 ppm	No effect; highest dose 7000 ppm			
			Mouse	80	Oral	4000 ppm	No effect; highest dose 4000 pppm			
			Mouse	80	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	4	Oral	5000 ppm	No effect; highest dose 5000 ppm			
			Rat	13	Oral	6000 ppm	No effect; highest dose 6000 ppm			
			Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	52	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	104	Oral	4000 ppm	No effect; highest dose 4000 ppm			
Evidence of general toxicity		Bodyweight	Dog	4	Oral	4000 ppm	Decreases in bodyweight in males ande females (2-3%)	Consistent statistically significant dose-dependent effects on bodyweight and bodyweight gain		N/A
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	3000 ppm	Bodyweight loss in males and reduced bodyweight gain in			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
							both sexes (-164% males; >-12% females)	in rats, mice and dogs		
			Mouse	4	Oral	7000 ppm	Marked reductions in bodyweight gain in males (-37% controls)			
			Mouse	13	Oral	7000 ppm	Reductions in bodyweight gain in males (-20% controls)			
			Mouse	80	Oral	4000 ppm	Reduced bodyweight from at week 77 (-18% males; -19% females)			
			Mouse	80	Oral	1500 ppm	Dose dependent decrease in bodyweight in males.			
			Rat	4	Oral	750/350 mg/kg/day	Bodyweight loss (-4.6%) and marked reductions in bodyweight gain in males (-22%)			
			Rat	4	Oral	3000 ppm	Dose dependent reduction in cumulative bodyweight gain (-7 to -17% in males; -9 to -11 in females)			
			Rat	4	Dermal	1000 mg/kg/day	No effect at limit dose			
			Rat	13	Oral	6000 ppm	Reduced group mean bodyweight gain (-18% males; -10% females)			
			Rat	2-Gen	Oral	4000 ppm	Reduction in parental pre-mating body weight (-9% males; -11% females). There was no effect during gestation or lactation.			
			Rat	52	Oral	4000 ppm	Reduced bodyweight gain (-7.6% males; -9.6% females)			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
			Rat	104	Oral	4000 ppm	Reduced bodyweight gain (-11% males; -15% females)			
		Liver weight (relative)	Dog	4	Oral	2000 ppm	>20% increase in males and females	Liver is the target organ for the compound. Consistent statistically significant dose dependent effects on liver weight with corroborative hepatocyte hypertrophy.		
			Dog	13	Oral	1250 ppm	No effect in relative weight. However slight increase in absolute liver weight at 1250 ppm in females			
			Dog	13	Oral	300 ppm	>17% increase in females and males at 1000 ppm			
			Mouse	4	Oral	1000 ppm	>13% increase in males and females at 3000 ppm			
			Mouse	13	Oral	1000 ppm	>10% increase in males and females at 3500 ppm			
			Mouse	80	Oral	4000 ppm	>12% increase in males and females			
			Mouse	80	Oral	1500 ppm	>11% dose-dependent increase in males and females on weeks 79-81.			
			Rat	4	Oral	3000 ppm	>13% increase in males and females.			
			Rat	4	Oral	750/350 mg/kg/day	>20% increase in males and females			
			Rat	4	Dermal	1000 mg/kg/day	No effect at limit dose			
			Rat	13	Oral	6000 ppm	>13% dose dependent increase in males and females			
			Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	52	Oral	4000 ppm	20% increase in females			
			Rat	104	Oral	4000 ppm	9% increase in males; no effect in females			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
		Liver (histopathology)	Dog	4	Oral	2000 ppm	Hepatocellular hypertrophy in mals and females at 4000 ppm			N/A
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	1000 ppm	Minimal to moderate centrilobular hepatocellular hypertrophy in males and females.			
			Mouse	4	Oral	3000 ppm	Slight centrilobular hepatocellular hypertrophy in males and females			
			Mouse	13	Oral	1000 ppm	Hepatocyte hypertrophy in males and females at 3500 ppm			
			Mouse	80	Oral	4000 ppm	Moderate hepatocyte hypertrophy in males and females			
			Mouse	80	Oral	1500 ppm	Hepatocellular hypertrophy in males and females			
			Rat	4	Oral	3000 ppm	Slight hepatocellular hypertrophy in males and females			
			Rat	4	Oral	750/350 mg/kg/day	Minimal to moderate hepatocellular hypertrophy in males and females			
			Rat	4	Dermal	1000 mg/kg/day	No effect at limit dose			
			Rat	13	Oral	6000 ppm	Minimal hepatocellular hypertrophy in males and females			
			Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			

	Grouping	Line(s) of evidence	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
			Rat	52	Oral	4000 ppm	Cytoplasmic inclusion bodies and enlargement of periportal hepatocytes in males. Hepatocyte hypertrophy in males and females			

Table 209: The lines of evidence for EAS modality in mammals

	Grouping	Effect Target	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
Integrated line of evidence for endocrine activity	None available									
Integrated lines of evidence for adversity	**EATS-mediated parameters**	None available								
	Parameter sensitive to, but not diagnostic of EAS	F1 Precoital interval	Rat	2-Gen	Oral	4000 ppm	No effect; highest dose tested 4000 ppm	No consistent effects on parameters considered sensitive to, but not diagnostic of EAS.	The weight of the evidence from *in vivo* studies indicates that dimethachlor does not have the potential to interact with the mammalian endocrine system. No EAS relevant adversity was noted in the GLP compliant studies.	EAS
		P Fertility	Rat	2-Gen	Oral	4000 ppm	No effect; highest dose tested 4000 ppm			
		F1 Fertility	Rat	2-Gen	Oral	4000 ppm	No effect; highest dose tested 4000 ppm			
		Litter size	Rabbit	2	Oral	350 mg/kg/day	No effect; highest dose 350 mg/kg/day			
		Litter size	Rat	1.5 (10 days)	Oral	700 mg/kg/day	No effect; highest dose 700 mg/kg/day			

	Grouping	Effect Target	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
		F1 Litter size	Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			
		F1 Foetal mortality	Rat	2-Gen	Oral	4000 ppm	No effect; there was an unusually high F1a pup loss between day 7-14, however, this was not replicated on the second mating or in the second generation and was not considered treatment related			
		Foetal mortality	Rat	1.5 (10 days)	Oral	700 mg/kg/day	No effect; highest dose 700 mg/kg/day			
		Foetal mortality	Rabbit	2	Oral	350 mg/kg/day	No effect; highest dose 350 mg/kg/day			
		F1 Gestational index	Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			
		F1 Litter weight	Rat	2-Gen	Oral	2000 ppm	Male pup weight was reduced (-13%) and female pup weight was reduced at 4000 ppm (-12%)			
		Litter weight	Rat	1.5 (10 days)	Oral	700 mg/kg/day	No effect; highest dose 700 mg/kg/day			

	Grouping	Effect Target	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
		Litter weight	Rabbit	2	Oral	350 mg/kg/day	No effect; highest dose 350 mg/kg/day			
Evidence of general toxicity		Bodyweight	Rabbit	2	Oral	350 mg/kg/day	Reduced bodyweight GD6-9, significantly reduced bodyweight gain across treatment period (-34% controls GD6-19)	Consistent statistically significant dose-dependent effects on bodyweight and bodyweight gain in rats, mice and dogs		N/A
			Rat	1.5 (10 days)	Oral	700 mg/kg/day	Reduced bodyweight gain (-17%) in pregnant females GD6-20			
			Dog	4	Oral	4000 ppm	Decreases in bodyweight in males ande females (2-3%)			
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	3000 ppm	Bodyweight loss in males and reduced bodyweight gain in both sexes (-164% males; >-12% females)			
			Mouse	4	Oral	7000 ppm	Marked reductions in bodyweight			

	Grouping	Effect Target	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
							gain in males (-37% controls)			
			Mouse	13	Oral	7000 ppm	Reductions in bodyweight gain in males (-20% controls)			
			Mouse	80	Oral	4000 ppm	Reduced bodyweight from at week 77 (-18% males; -19% females)			
			Mouse	80	Oral	1500 ppm	Dose dependent decrease in bodyweight in males.			
			Rat	4	Oral	750/350 mg/kg/day	Bodyweight loss (-4.6%) and marked reductions in bodyweight gain in males (-22%)			
			Rat	4	Oral	3000 ppm	Dose dependent reduction in cumulative bodyweight gain (-7 to -17% in males; -9 to -11 in females)			
			Rat	4	Dermal	1000 mg/kg/day	No effect at limit dose			
			Rat	13	Oral	6000 ppm	Reduced group mean bodyweight gain (-18%			

	Grouping	Effect Target	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
							males; -10% females)			
			Rat	2-Gen	Oral	4000 ppm	Reduction in parental pre-mating body weight (-9% males; -11% females). There was no effect during gestation or lactation.			
			Rat	52	Oral	4000 ppm	Reduced bodyweight gain (-7.6% males; -9.6% females)			
			Rat	104	Oral	4000 ppm	Reduced bodyweight gain (-11% males; -15% females)			
		Liver weight (relative)	Dog	4	Oral	2000 ppm	>20% increase in males and females	Liver is the target organ for the compound. Consistent statistically significant dose dependent effects on liver weight with corroborative hepatocyte hypertrophy.		
			Dog	13	Oral	1250 ppm	No effect in relative weight. However slight increase in absolute liver weight at 1250 ppm in females			
			Dog	13	Oral	300 ppm	>17% increase in females and males at 1000 ppm			
			Mouse	4	Oral	1000 ppm	>13% increase in males and			

	Grouping	Effect Target	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
							females at 3000 ppm			
			Mouse	13	Oral	1000 ppm	>10% increase in males and females at 3500 ppm			
			Mouse	80	Oral	4000 ppm	>12% increase in males and females			
			Mouse	80	Oral	1500 ppm	>11% dose-dependent increase in males and females on weeks 79-81.			
			Rat	4	Oral	3000 ppm	>13% increase in males and females.			
			Rat	4	Oral	750/350 mg/kg/day	>20% increase in males and females			
			Rat	4	Dermal	1000 mg/kg/day	No effect at limit dose			
			Rat	13	Oral	6000 ppm	>13% dose dependent increase in males and females			
			Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	52	Oral	4000 ppm	20% increase in females			
			Rat	104	Oral	4000 ppm	9% increase in males; no effect in females			
		Liver (histopathology)	Dog	4	Oral	2000 ppm	Hepatocellular hypertrophy in mals and			

	Grouping	Effect Target	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
							females at 4000 ppm			
			Dog	13	Oral	1250 ppm	No effect; highest dose 1250 ppm			
			Dog	13	Oral	1000 ppm	Minimal to moderate centrilobular hepatocellular hypertrophy in males and females.			
			Mouse	4	Oral	3000 ppm	Slight centrilobular hepatocellular hypertrophy in males and females			
			Mouse	13	Oral	1000 ppm	Hepatocyte hypertrophy in males and females at 3500 ppm			
			Mouse	80	Oral	4000 ppm	Moderate hepatocyte hypertrophy in males and females			
			Mouse	80	Oral	1500 ppm	Hepatocellular hypertrophy in males and females			
			Rat	4	Oral	3000 ppm	Slight hepatocellular hypertrophy in males and females			
			Rat	4	Oral	750/350 mg/kg/day	Minimal to moderate			

	Grouping	Effect Target	Species	Exposure (weeks)	Route of exposure	Effect dose	Observed effects	Assessment of each line of evidence	Assessment of the integrated lines of evidence	Modality
							hepatocellular hypertrophy in males and females			
			Rat	4	Dermal	1000 mg/kg/day	No effect at limit dose			
			Rat	13	Oral	6000 ppm	Minimal hepatocellular hypertrophy in males and females			
			Rat	2-Gen	Oral	4000 ppm	No effect; highest dose 4000 ppm			
			Rat	52	Oral	4000 ppm	Cytoplasmic inclusion bodies and enlargement of periportal hepatocytes in males. Hepatocyte hypertrophy in males and females			
			Rat	104	Oral	4000 ppm				

RMS' conclusions on EAS modality

The RMS agrees with the Applicant's conclusions.

A dataset is considered to have sufficiently investigated EAS related adversity in relation to mammals if the parameters investigated in a two-generation reproductive toxicity study (OECD TG 416) implicit to the 2001 revision of this guideline have been assessed (EFSA-ECHA 2018). Since the two-generation toxicity study with dimethachlor does not consider all parameters required for compliance to the current guideline (oestrous cyclicity, quantitative ovarian follicle count, sperm parameters and sexual maturation were not specifically investigated), in accordance with the EFSA-ECHA (2018) Guidance, EAS related adversity has not been sufficiently investigated and further *in vitro* and *in vivo* mechanistic data is triggered.

RMS' conclusions on thyroid modality

A dataset is considered to have sufficiently investigated thyroid related adversity in relation to mammals if the parameters investigated in OECD TG 407, 408, 409 (and/or the one-year dog study, if available), 416 and 453 have been assessed. Assessment of the potential for dimethachlor to alter thyroid related parameters (histology and/or weight) has been conducted in studies spanning a range of durations (from 28-days to 104-weeks), in the mouse, rat and dog, and through multiple exposure routes (see data reviews in Section 4). RMS agrees with the Applicant that although thyroid hormones gave not been measured, the potential for thyroid-related effects in mammals has been sufficiently addressed and no further data is required to determine that there is no concern for thyroid adversity in the mammalian toxicity database for dimethachlor.

RMS' overall conclusion on the ED assessment

The available data on dimethachlor do not indicate effects consistent with endocrine disruption. Thyroid parameters have been sufficiently investigated and the ED criteria are not met for the T modality. However, in accordance with the EFSA-ECHA (2018) Guidance, EAS-mediated parameters have not been sufficiently investigated in vivo. Applying this Guidance Document, in vitro and *in vivo* mechanistic studies are triggered to further investigate EAS modalities in the absence of a modern two-generation study.

In accordance with the EFSA-ECHA (2018) Guidance, the following *in vitro* and *in vivo* mechanistic studies are triggered for EAS modalities:

1) *In vitro* steroidogenesis assay (OECD 456)

2) *In vitro* ER transactivation assay (OECD 455)

3) *In vitro* AR transactivation assay (OECD 458)

4) Uterotrophic assay (OECD 440)

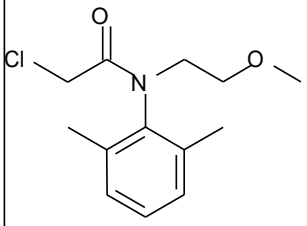
5) Hershberger assay (OECD 441)

2.11 PROPOSED HARMONISED CLASSIFICATION AND LABELLING ACCORDING TO THE CLP CRITERIA *[SECTIONS 1-6 OF THE CLH REPORT]*

2.11.1 Identity of the substance [section 1 of the CLH report]

2.11.1.1 Name and other identifiers of the substance

Table 210: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	2-chloro-N-(2,6-dimethylphenyl)-N-(2-methoxyethyl)acetamide 2-chloro-N-(2-methoxyethyl)acet-2',6'-xylidide
Other names (usual name, trade name, abbreviation)	Dimethachlor CGA17020
ISO common name (if available and appropriate)	Dimethachlor
EC number (if available and appropriate)	256-625-6
EC name (if available and appropriate)	
CAS number (if available)	50563-36-5
Other identity code (if available)	CIPAC number 688
Molecular formula	$C_{13}H_{18}ClNO_2$
Structural formula	
SMILES notation (if available)	CC1=C(C(=CC=C1)C)N(CCOC)C(=O)CCl
Molecular weight or molecular weight range	255.74 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not relevant
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not relevant
Degree of purity (%) (if relevant for the entry in Annex VI)	Min. 95 %

2.11.1.2 Composition of the substance

Table 211: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Dimethachlor	>95%	Acute Tox. 4 (H302) Skin Sens. 1 (H317) Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410)	Acute Tox. 4 (H302) Skin Sens. 1 (H317) Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410)

Table 212: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Details on impurities are confidential information (see confidential Volume 4 or Confidential Annex to CLH report)				

Table 213: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
Not relevant					

Table 214: Test substances (non-confidential information)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used

2.11.2 Proposed harmonized classification and labelling

Proposed harmonised classification and labelling according to the CLP criteria

Table 215: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	**Hazard statement Code(s)**	**Pictogram, Signal Word Code(s)**	**Hazard statement Code(s)**	**Suppl. Hazard statement Code(s)**		
Current Annex VI entry	616-031-00-3	dimethachlor (ISO); 2-chloro-*N*-(2,6-dimethylphenyl)-*N*-(2-methoxyethyl)acetamide	256-625-6	50563-36-5	Acute Tox. 4 * Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H302 H317 H400 H410	GHS07 GHS09 Wng	H302 H317 H410			
Dossier submitters proposal	616-031-00-3	dimethachlor (ISO); 2-chloro-*N*-(2,6-dimethylphenyl)-*N*-(2-methoxyethyl)acetamide	256-625-6	50563-36-5	**Retain** Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1 **Add** Carc. 2 **Modify** Acute Tox. 4	**Retain** H302 H317 H400 H410 **Add** H351	**Retain** GHS07 GHS09 Wng **Add** GHS08	**Retain** H302 H317 H410 **Add** H351		**Add** M = 10 M = 10	
Resulting entry in Annex VI if adopted by RAC and agreed by Commission	616-031-00-3	dimethachlor (ISO); 2-chloro-*N*-(2,6-dimethylphenyl)-*N*-(2-methoxyethyl)acetamide	256-625-6	50563-36-5	Carc. 2 Acute Tox. 4 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H351 H302 H317 H400 H410	GHS08 GHS07 GHS09 Wng	H351 H302 H317 H410		M = 10 M = 10	

Additional hazard statements / labelling

Table 216: Reason for not proposing harmonised classification and status under CLH public consultation

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Explosives	Data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Hazard class not applicable	No
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Hazard class not applicable	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Data conclusive but not sufficient for classification	Yes
Self-reactive substances	Data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Data conclusive but not sufficient for classification	Yes
Self-heating substances	Data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	Yes
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Data conclusive but not sufficient for classification	Yes
Organic peroxides	Data conclusive but not sufficient for classification	Yes
Corrosive to metals	Data conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	Harmonised classification proposed	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Data conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	Data conclusive but not sufficient for classification	Yes
Respiratory sensitisation	Data conclusive but not sufficient for classification	Yes
Skin sensitisation	Harmonised classification proposed	Yes
Germ cell mutagenicity	Data conclusive but not sufficient for classification	Yes
Carcinogenicity	Harmonised classification proposed	Yes
Reproductive toxicity	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-single exposure	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-repeated exposure	Data conclusive but not sufficient for classification	Yes
Aspiration hazard	Hazard class not applicable	No
Hazardous to the aquatic environment	Harmonised classification proposed	Yes

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Hazardous to the ozone layer	Data conclusive but not sufficient for classification	Yes

2.11.3. History of the previous classification and labelling

The harmonized classification and labelling of dimethachlor has been considered previously in the EU. The existing entry in Annex VI of CLP Regulation (EU) 1272/2008 is:

Acute Tox. 4 *, H302

Skin Sens. 1, H317

Aquatic Acute 1, H400

Aquatic Chronic 1, H410

2.11.4. Identified uses

Dimethachlor is a herbicide used for many years in Europe, primarily in oilseed rape. Form more details, please refer to section 1.5 Detailed uses of the plant protection product.

2.11.5. Data sources

The data source is the supplementary dossier submitted by the applicant in support of the renewal of approval of dimethachlor as an active substance under Regulation (EU) 1107/2009.
No REACH registration dossier was available for the substance dimethachlor (ISO); 2-chloro-N-(2,6-dimethylphenyl)-N-(2-methoxyethyl)acetamide on 27.03.2023.

2.12 RELEVANCE OF METABOLITES IN GROUNDWATER

2.12.1. STEP 1: Exclusion of degradation products of no concern

None of metabolites CGA42443, CGA50266, CGA102935, CGA354742, CGA369873, CGA373464, SYN530561 and SYN547047 can be excluded as a degradation product of no concern.

2.12.2. STEP 2: Quantification of potential groundwater contamination

A summary of the potential groundwater contamination at tiers 1, 3 and 4 is presented below.

TIER	Study	CGA 42443	CGA 50266	CGA 102935	CGA 354742	SYN 547047	CGA 369873	CGA 373464	SYN 530561
1	FOCUS modelling	**Overall 80th Percentile PEC_{GW} at 1 m Soil Depth [µg/L]**							
		0.679	19.0	0.929	20.8	0.518	24.5	0.193	1.23
3	Lysimeter	**Annual average concentrations in leachate [µg/L]**							
		-	36.2	-	35.1	11.3	2.5	3.3	2.1
4	Groundwater monitoring	**90th percentile Tolerance Interval [µg/L]**							
Germany		0.025	0.15	0.025	4.42	0.025	4.89	0.025	0.025
Lithuania		**0.025**	**3.98**	**0.17**	**9.90**	**0.40**	**5.22**	**0.025**	**0.025**

France	0.025	0.025	0.025	0.025	<LOQ	0.17	0.025	0.025
ADES	0.025	0.18	0.025	0.21	0.025	0.37	0.025	0.025

2.12.3. STEP 3: Hazard assessment – identification of relevant metabolites

STEP 3, Stage 1: screening for biological activity

None of metabolites CGA42443, CGA50266, CGA102935, CGA354742, CGA369873, CGA373464, SYN530561 and SYN547047 are biologically active.

STEP 3, Stage 2: screening for genotoxicity

Genotoxicity studies have been performed for CGA50266, CGA354742, CGA369873, CGA373464, SYN530561, SYN547047 CGA102935 and CGA42443. There was no evidence of mutagenicity or clastogenicity in any of these metabolites tested in any of the assays and therefore, all eight of the metabolites are considered to be non-genotoxic.

STEP 3, Stage 3: screening for toxicity

Toxicity data

Dimethachlor is of low acute toxicity, and acute studies conducted on CGGA50266 and CGA354742 showed that these metabolites are less toxic at comparable dose levels than the parent compound (dimethachlor, CGA17020). Short term studies were performed for CGA50266, CGA354742, CGA369873, CGA42443 and CGA373464. Some effects seen with metabolites were different to parent, affecting the kidney, adrenal, thyroid and bone marrow. However, in comparison to the parent at comparable dose levels, the metabolites CGA50266, CGA354742 CGA369873, CGA42443 and CGA373464 are considered to be less toxic. No repeat dose toxicity data is available for SYN530561, SYN547047 and CGA102935 however due to the similarity in chemical structure between these metabolites and other ground-water metabolites where general toxicity data has been generated, the toxicity concerns for SYN530561, SYN547047 and CGA102935 are addressed using a read-across strategy. Therefore, it could be concluded that these metabolites are similarly or less toxic than parent at comparable dose levels.

Nevertheless, since for the parent (dimethachlor, CGA17020) the classification for carcinogenicity (Cat 2) is proposed by the RMS, **convincing evidence must be provided by the applicant that the metabolites will not lead to any risk of carcinogenicity if their concentrations exceed the maximum permissible concentration (0.1 µg/l) for groundwater**, according to the Guidance Document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC, for parent active substances classified as category 2 carcinogens (Carc. Cat. 2; H351).

Ecotoxicity data

Green algae have been identified as the most sensitive aquatic species to dimethachlor. Consequently, the dimethachlor metabolites CGA42443, CGA102935, CGA50266, CGA354742, CGA369873, CGA373464, SYN530561 and SYN547047 have also been tested in standard tests with freshwater green algae. All metabolites are at least approximately 3000-fold less active against *Pseudokirchneriella subcapitata* than dimethachlor. Therefore, CGA42443, CGA102935, CGA50266, CGA354742, CGA369873, CGA373464, SYN530561 and SYN547047 are not considered to be of ecotoxicological concern.

Since the potential groundwater contamination described in step 2 exceeds 0.1 µg/L and convincing evidence that the metabolites will not lead to any risk of carcinogenicity has not been provided, these metabolites did not pass stage 3 of step 3 and they are not subject to an exposure and/or risk assessment (step 4 and step 5) according to the Guidance Document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC.

2.12.4. STEP 4: Exposure assessment – threshold of concern approach

Not applicable.

2.12.5. STEP 5: Refined risk assessment

Not applicable.

2.12.6. Overall conclusion

Experimental data and/or considerations based on structural features and similarities demonstrate that

- none of the metabolites are biologically (herbicidally) active
- none of the metabolites are genotoxic

However, the parent (dimethachlor, CGA17020) the classification for carcinogenicity (Cat 2). Since the potential groundwater contamination described in step 2 exceeds 0.1 µg/L and convincing evidence that the metabolites will not lead to any risk of carcinogenicity has not been provided, these metabolites did not pass stage 3 of step 3 and they are not subject to an exposure and/or risk assessment (step 4 and step 5) according to the Guidance Document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC.

2.13 CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

The active substance dimethachlor is not a mixture of isomers. Therefore no information is presented.

2.13.1. Identity and physical chemical properties

Not applicable.

2.13.2. Methods of analysis

Not applicable.

2.13.3. Mammalian toxicity

Not applicable.

2.13.4. Operator, Worker, Bystander and Resident exposure

Not applicable.

2.13.5. Residues and Consumer risk assessment

Not applicable.

2.13.6. Environmental fate

Not applicable.

2.13.7. Ecotoxicology

Not applicable.

2.14 RESIDUE DEFINITIONS

2.14.1. Definition of residues for exposure/risk assessment

Food of plant origin: dimethachlor (pulses and oilseeds only)

Food of animal origin: Not required

Soil: dimethachlor, CGA 50266, CGA 102935, CGA 354742 and SYN 547047. If anaerobic conditions occur CGA 42443.

Groundwater: dimethachlor, CGA 50266, CGA 354742, CGA 102935, SYN 528702, CGA 369873, CGA 373464, CGA 42443 and SYN 530561

Surface water: dimethachlor, CGA 50266, if anaerobic soil conditions occur CGA 42443

Sediment: dimethachlor

Air: dimethachlor

2.14.2. Definition of residues for monitoring

Food of plant origin: dimethachlor (pulses and oilseeds only)

Food of animal origin: Not required

Soil: dimethachlor, except in territories where anaerobic soil conditions cannot be excluded where a data gap needs to be filled before this definition can be finalised.

Groundwater: At least dimethachlor, but data gaps need to be filled before this definition can be finalised.

Surface water: dimethachlor, except in territories where anaerobic soil conditions cannot be excluded where a data gap needs to be filled before this definition can be finalised.

Sediment: dimethachlor

Air: dimethachlor

Level 3

Dimethachlor

3. PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1. BACKGROUND TO THE PROPOSED DECISION

3.1.1. Proposal on acceptability against the decision making criteria – Article 4 and annex II of regulation (EC) No 1107/2009

Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.			Active substance: Dimethachlor Representative products: TERIDOX 500 EC
Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted		X	
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.	X		(b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision: The available data on dimethachlor do not indicate effects consistent with endocrine disruption. However, in accordance with the EFSA-ECHA (2018) Guidance, EAS-mediated parameters have not been sufficiently investigated in vivo. Therefore, further *in vitro* and *in vivo* mechanistic data is triggered and proposed by the Applicant to be generated (see level 2.10).
Restrictions on approval				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.	X		Maximum amount of the active substance per season per hectare must not exceed 1.0 kg every 3 years on the same field. The protection of the groundwater, when the active substance is applied in regions with vulnerable soil and/or climatic conditions. Conditions of authorisation shall include risk mitigation measures and monitoring programmes shall be initiated to verify potential groundwater contamination from metabolites CGA 50266, CGA 354742, CGA 369873, CGA 102935 and SYN 547047 in vulnerable zones, where appropriate.

Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	X		See detailed evaluation in Volume 3, sections 8 and 9.
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.			The dossier contains all of the information on dimethachlor necessary to conduct risk assessment and for enforcement purposes. Animal metabolism and feeding studies are not required and thus default MRLs are applicable. Since residues of dimethachlor were shown to be below the limit of quantification in the representative use oilseed rape, concentration of residues in processed commodities is not expected nor is there any risk for consumers. See detailed evaluation in Volume 3 – B.7 (AS).
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.			*[Explain if this applies to all or some of the representative uses/use scenarios/products]*
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	X		Sufficient information on efficacy of dimethachlor was provided. For details please see Level 2, Section 2.3.
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	Yes		The toxicological, ecotoxicological or environmental relevance of metabolites can be established.

Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	X		Minimum purity of dimethachlor as manufactured is 950 g/kg. All impurities greater than 1 g/kg are determined and expressed with maximum content. One relevant impurity is within acceptable limit.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.		X	There is no FAO specification for dimethachlor.
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted		X	There is no FAO specification for dimethachlor.
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	X		Analytical methods for the determination of dimethachlor and its manufacturing impurities in technical material were evaluated and considered acceptable according to current test guidelines. All relevant data is considered adequate for approval within terms of methods of analysis.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	X		Adequate methods and ILVs are available to monitor the respective current residue definition in plant material, soil, drinking water, surface water and air (Volume 1 – Level 2, point 2.5.2.) This applies to the representative use on oilseed rape (pre- and/or post-emergance application).
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		
Impact on human health				
Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	X		**ADI**: **0.1 mg/kg bw/day**, based on 2 year rat study and supported by 90 day dog study, and by using a safety factor of 100 (see level 2.6.10.1). **ARfD**: **0.5 mg/kg bw/day**, based on developmental toxicity study in rats, and by using a safety factor of 100 (see level 2.6.10.2). **AOEL**: **0.1 mg/kg bw/day**, based on 90 day dog study, and by using a safety factor of 100 (see level 2.6.10.3).

				AAOEL: **0.5 mg/kg bw/day**, based on developmental toxicity study in rats, and by using a safety factor of 100 (see level 2.6.10.4). As the systemic absorption of dimethachlor after oral administration was determined to be ≥ 94 %, there is no requirement to adjust for absorption.
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		X	There is no evidence that dimethachlor is genotoxic when assessed in a range of in vitro and in vivo assays. There is no evidence that there is any risk of genotoxic effects in humans exposed to dimethachlor (see level 2.6.4).
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**		X	Based on limited evidence of carcinogenicity in animal studies, namely treatment-related increase in incidence of nasopharingeal adenomas arising from nasal respiratory epithelium in male rats, for which mode of action is not known and relevance for humans cannot be ruled out, classification for **Carc Cat 2 (H351)** is proposed by the RMS (see level 2.6.5).
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not applicable.
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for**		X	There were no adverse effects of dimethachlor on the sexual function and fertility of parental rats at dose levels that induced toxicity, and there were no adverse effects of dimethachlor on the development of the offspring. In developmental toxicity studies in the rat and rabbit, no embryotoxic, foetotoxic or teratogenic effects of treatment were observed. Minor effects in

	classification, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**			developmental delay seen only in the rat were considered secondary to maternal toxicity. There are no human data for dimethachlor. RMS, therefore, proposes no classification for dimethachlor for reproductive toxicity (see level 2.6.6).
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not applicable.
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE identified as having endocrine disrupting properties** in accordance with the provisions of point 3.6.5 in Annex II of Regulation (EC) No 1107/2009		X	The available data on dimethachlor do not indicate effects consistent with endocrine disruption. However, in accordance with the EFSA-ECHA (2018) Guidance, EAS-mediated parameters have not been sufficiently investigated in vivo. Therefore, further in vitro and in vivo mechanistic data is triggered and proposed by the Applicant to be generated (see level 2.10).
ii)	Linked to above identification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			*[if yes provide a brief explanation of conditions of use and cross refer to the section containing full details to support the contention of negligible exposure]*
Fate and behaviour in the environment				
Persistent organic pollutant (POP)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		No	Dimethachlor does not fulfil the criteria for classification as a POP. The P criterion is not fulfilled - Soil compartment: below criteria (DT_{50} (soil) = 19.8 days (longest non-normalised laboratory DT_{50}, SFO best fit))

				- Aquatic compartment: below criteria based on a weight of evidence approach (the analysis of test systems characteristics) (See Section 2.8.1 (Level 2)) Dimethachlor is not expected to have long-range transport potential because the estimated half-life in air is <0.5 days, i.e. below the criterion of 2 days.
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		No	Dimethachlor does not fulfil two of the criteria for classification as a PBT. The P criterion is not fulfilled - Soil compartment: below criteria - Aquatic compartment: below criteria based on a weight of evidence approach (the analysis of test systems characteristics) (See Section 2.8.1 (Level 2)) The B criterion is not fulfilled. Dimethachlor log Pow is below 3 (2.17).
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		No	Dimethachlor does not fulfil both of the criteria for classification as a vPvB. The P criterion is not fulfilled - Soil compartment: below criteria - Aquatic compartment: below criteria based on a weight of evidence approach (the analysis of test systems characteristics) (See Section 2.8.1 (Level 2)) The B criterion is not fulfilled. Dimethachlor log Pow is below 3 (2.17).
Ecotoxicology				
		Yes	No	
i	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of			A low acute and chronic risk to birds was identified for all intended uses based on a higher tier risk assessment. In the higher tier risk assessment PD refinemet was used in the acute risk, in the long-term risk justification for focal species, PD and PT refinement, and foliage residue dissipation rate of dimethachlor was used. The risk to birds from secondary poisoning and contaminated drinking water was assessed to be low.

	organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.			For mammals the acute risk was indicated to be low. However, a potential high long-term risk was calculated for all intended uses at tier 1. In the higher tier risk assessment foliage residue dissipation rate of dimethachlor was used. The risk to fish-eating mammals and to mammals from uptake of contaminated drinking water was identified to be low. A high risk to algae and aquatic macropytes was identified. Risk mitigation measures are needed (see Table 150). Some of the scenarios could not be resolved. Laboratory studies on acute oral and contact toxicity and on chronic toxicity to adult honeybees and larvae were conducted. Risk for chronic adult oral toxicity was recognised. For the higher tier risk assessment results from residue study in pollen and nectar was used. The risk assessment for other non-target arthropods was assessed as low. The risk for earthworms and other soil macro-organisms was assessed as low. The risk assessment performed for nitrogen transformation resulted in a low risk. The risk assessment performed for non-target plants indicated risk, futher calculations with buffer zones and drift reduction nozzles were performed. Risk to non-target plants was acceptable with the use of risk mitigation measures. For a detailed summary please refer to Level 2, Section 2.9.
ii	It is considered that, the substance **SHOULD BE identified as having endocrine disrupting properties** that may cause adverse effects on non-target organisms in accordance with the provisions of point 3.8.2 in Annex II of Regulation (EC) No 1107/2009.			The available dataset is insufficient to conclude on ED properties of dimethachlor.
iii	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.			*[Explain if this applies to all or some of the representative uses/use scenarios/products]*

iv	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.			Laboratory studies on acute oral and contact toxicity and on chronic toxicity to adult honeybees and larvae were conducted. Based on the available data an acceptable risk to adult honeybees and honeybee larvae for all GAP uses was identified. For a detailed summary please refer to Level 2, Section 2.9.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	Yes		Definition of the residue in crops (for monitoring and risk assessment purposes): Dimethachlor (pulses and oilseeds only) Definition of the residue in animal products (for monitoring and risk assessment purposes): Not required Residue definition of environmental components (for exposure/risk assessment): **Soil:** dimethachlor, CGA 50266, CGA 102935, CGA 354742 and SYN 547047. If anaerobic conditions occur CGA 42443. **Groundwater:** dimethachlor, CGA 42443, CGA 50266, CGA 354742, CGA 102935, SYN 547047, CGA 369873, CGA 373464 and SYN 530561. **Surface water:** dimethachlor, CGA 50266, if anaerobic soil conditions occur CGA 42443 **Sediment:** dimethachlor **Air:** dimethachlor
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction	Yes		For dimethachlor, the PEC_{GW} simulations did not reach or exceed the parametric trigger value of 0.1 µg/L in any FOCUS gw scenario for the intended uses on winter and spring oilseed rape.

	products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.			Significant soil metabolites (CGA50266, CGA102935 and CGA354742), plus metabolites CGA369873, CGA373464 and SYN530561 observed in lysimeter leachate exceeded 0.1 µg/L for all uses in one or more scenarios except for CGA42443 on winter oilseed rape (750 g a.s./ha, BBCH 20) and SYN547047 on winter oilseed rape (750 and 1000 g a.s./ha, BBCH 20) and spring oilseed rape (750 g a.s./ha, BBCH 00). Since the potential groundwater contamination described in step 2 exceeds 0.1 µg/L and convincing evidence that the metabolites will not lead to any risk of carcinogenicity has not been provided, these metabolites did not pass stage 3 of step 3 and they are not subject to an exposure and/or risk assessment (step 4 and step 5) according to the Guidance Document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC.

3.1.2. Proposal – Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution		X	

3.1.3. Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** If the active substance is not a micro-organism, in particular it is considered that: (a) the substance **should NOT be classified or proposed for classification** in accordance to Regulation (EC) No 1272/2008 as any of the following:		X	Dimethachlor does not fulfil the criteria for low risk.

	— carcinogenic category 1A, 1B or 2, — mutagenic category 1A, 1B or 2, — toxic to reproduction category 1A, 1B or 2, — skin sensitiser category 1, — serious damage to eye category 1, — respiratory sensitiser category 1, — acute toxicity category 1, 2 or 3, — specific Target Organ Toxicant, category 1 or 2, — toxic to aquatic life of acute and chronic category 1 on the basis of appropriate standard tests, — explosive, — skin corrosive, category 1A, 1B or 1C; (b) it has **not been identified as priority substance under Directive 2000/60/EC**; (c) it is **not deemed to be an endocrine disruptor** in accordance to Annex II of Regulation (EC) No 1107/2009; (d) it **has no neurotoxic or immunotoxic effects**; (e) it **is not persistent** (half-life in soil is more than 60 days) or its **bio-concentration factor is lower than 100**. (f) it is a **semiochemical** and verifies points (a) to (d). Paragraph (e) doesn't apply to naturally occurring active substances. If the active substance is a micro-organism, in particular it is considered that at strain level the micro-organism has not demonstrated multiple resistance to anti-microbials used in human or veterinary medicine. If the active substance is a baculovirus, in particular it has not demonstrated adverse effects on non-target insects.			

3.1.4. List of studies to be generated, still ongoing or available but not peer reviewed

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
Identity of the active substance or formulation				
Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
Data on uses and efficacy				
Data on handling, storage, transport, packaging and labelling				
Methods of analysis				
None.				

Toxicology and metabolism				
CGA42443 - *In Vitro* L5178Y Gene Mutation Assay at the hprt locus				Final report finished but not evaluated.
SYN530561 - *In Vitro* L5178Y Gene Mutation Assay at the hprt locus				Final report finished but not evaluated.
CGA048088 - *In vitro* comparative metabolism of dimethachlor sulfoxide (CGA048088) in human and rat liver and nasal microsomes				Final report finished but not evaluated.
In vitro steroidogenesis assay (OECD 456)		X		
In vitro ER transactivation assay (OECD 455)		X		
In vitro AR transactivation assay (OECD 458)		X		
Uterotrophic assay (OECD 440)		X		
Hershberger assay (OECD 441)		X		
Residue data				
K-CA 6.1/02 Mahlow S., 2019a Dimethachlor: Storage Stability of Residues of Metabolites SYN551032 and CGA048090 in Crop Matrices Stored Frozen for up to Two Years and Six Months Interim report Syngenta Report No. S19-00754 Syngenta File No. SYN551032_10002 GLP, unpublished	Submitted for the purpose of renewal. Storage stability of metabolite was not yet demonstrated.		Final report expected October 2021.	
Environmental fate and behaviour				

Ecotoxicology				
Dimethachlor – Foliar Residue Decline Study on Winter Oilseed Rape in Germany, Northern France, the United Kingdom and Spain in 2019/2020				X
21-day fish screening assay (OECD 230) in the Fathead minnow.		X		
Amphibian Metamorphosis Assay (OECD 231)		X		

3.1.5. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	**Relevance in relation to representative use(s)**
Endocrine disruption – EAS modality: Since the two-generation toxicity study with dimethachlor does not consider all parameters required for compliance to the current guideline (oestrous cyclicity, quantitative ovarian follicle count, sperm parameters and sexual maturation were not specifically investigated), in accordance with the EFSA-ECHA (2018) Guidance, EAS related adversity has not been sufficiently investigated and further *in vitro* and *in vivo* mechanistic data is triggered.	*All uses.*

3.1.6. Critical areas of concern

An issue is listed as a critical area of concern:
(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	Relevance in relation to representative use(s)
Risk to aquatic organisms	All uses.
Risk to non-target plants	All uses.

3.1.7. Overview table of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)
All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		Use " Winter oilseed rape" (X[1])	Use " Spring oilseed rape" (X[1])
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial vertebrates	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised		
Risk to aquatic organisms	Risk identified	X	X
	Assessment not finalised		
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached		
	Parametric value of 10µg/L[(a)] breached	X	X
	Assessment not finalised		
Comments/Remarks			

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.
(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

3.1.8. Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	**Justification**
Carcinogenicity	Discussion on the justification for Carc Cat 2 proposed by the RMS, especially considering different types of nasopharyngeal tissue affected by neoplasia due to dimethachlor and other chloroacetanilides exposure in animals.

Environmental fate and behaviour	Calculation of "regulatory endpoints" from groundwater monitoring results. Irrespective whether a 90th percentile concentration from a given set of monitoring results may be considered a valid regulatory endpoint (or not), we want to stress that there are numerous statistical approaches on how to calculate a certain percentile from a given data set. This issue is not trivial as it may have a strong impact on the percentile concentration obtained, particularly at more extreme (high and low) percentiles. We are of the opinion that the methodology on how to calculate a certain (e.g., 90th) percentile from a given set of monitoring results needs further agreement amongst risk assessors.

3.1.9. Critical issues on which the Co RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	**Opinion of Co-RMS**	**Opinion of RMS**
The degradation of dimethachlor is not pH depandent.	The Co-RMS is not fully convinced that degradation of dimethachlor is not pH dependent. This may be elaborated more in detail.	From the indicative assessment, it seems likely that degradation of dimethachlor in soil is correlated with soil pH. This findings is supported by the Pearson's correlation test that revealed a moderate to high negative correlation at the $p = 0.05$ significance level. The Kendall's rank correlation was not significant at the $p = 0.05$ significance level. Nevertheless, the RMS HR considers that the first two indicators (graphical correlation and Pearson's correlation test) are not sufficient to confirm a pH-dependency of the degradation of dimethachlor in soil.

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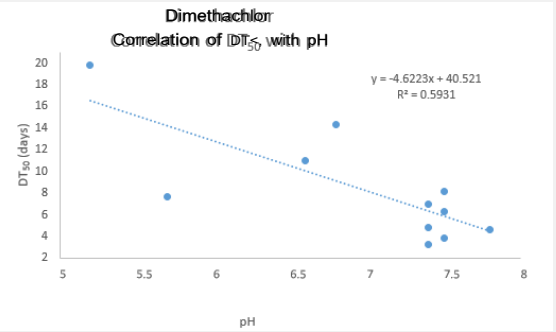
<td>


RMS HR did an own statistical analysis to evaluate correlation between degradation rates and pH value of the tested soils. Correlations among the data were tested using Pearson and Kendall's rank correlation test and also visually.
<table>
<tr><th>Correlation</th><th colspan="2">Pearson's product-moment corr.</th><th colspan="2">Kendall's rank correlation test</th></tr>
<tr><th></th><th>correlation</th><th>p-value</th><th>tau</th><th>p-value</th></tr>
<tr><td>soil pH × DT_{50}</td><td>-0.770</td><td>0.006</td><td>-0.482</td><td>0.056</td></tr>
</table>
The trendline indicated that degradation of dimethachlor in soil is marginally pH-dependent. This findings is supported by the Pearson's correlation test that revealed a significant correlation at the $p = 0.05$ significance level. According to Chart presented above (R^2 value of 0.593) and the Pearson's correlation test that revealed a moderate to high negative correlation at the $p = 0.05$ significance level, and the Kendall's rank correlation which is not significant at the $p = 0.05$ significance level, RMS is of the opinion that the degradation of dimethachlor is not pH dependent.
</td>
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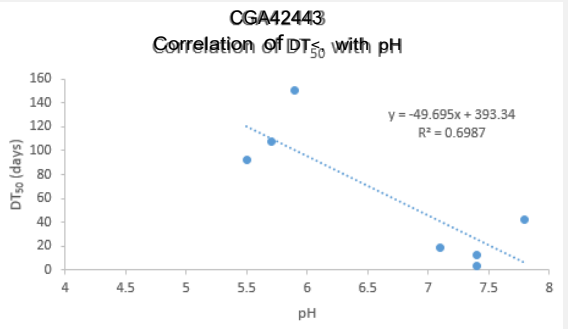
<tr>
<td>The degradation of CGA 42443 is not pH depandent.</td>
<td>The Co-RMS is not fully convinced that degradation of CGA 42443 is not pH dependent. This may be elaborated more in detail.</td>
<td>
From the indicative assessment, it seems likely that degradation of metabolite CGA42443 in soil is correlated with soil pH.
This findings is supported by the Pearson's correlation test that revealed a high negative correlation at the $p = 0.05$ significance level. The Kendall's rank correlation was not significant at the $p = 0.05$ significance level. Nevertheless, the RMS HR considers that the first two indicators (graphical correlation and Pearson's correlation test) are not sufficient to confirm a pH-dependency of the degradation of dimethachlor in soil.


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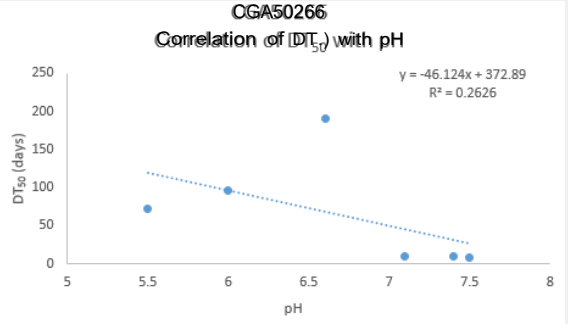
<td>RMS HR did an own statistical analysis to evaluate correlation between degradation rates and pH value of the tested soils. Correlations among the data were tested using Pearson and Kendall's rank correlation test and also visually.
<table>
<tr><th rowspan="2">Correlation</th><th colspan="2">Pearson's product-moment corr.</th><th colspan="2">Kendall's rank correlation test</th></tr>
<tr><th>correlation</th><th>p-value</th><th>tau</th><th>p-value</th></tr>
<tr><td>soil pH × DT_{50}</td><td>-0.836</td><td>0.019</td><td>-0.390</td><td>0.288</td></tr>
</table>
The trendline indicated that degradation of metabolite CGA42443 in soil is marginally pH-dependent. This findings is supported by the Pearson's correlation test that revealed a significant correlation at the $p = 0.05$ significance level.
According to Chart presented above (R^2 value of 0.699) and the Pearson's correlation test that revealed a high negative correlation at the $p = 0.05$ significance level, and the Kendall's rank correlation which is not significant at the $p = 0.05$ significance level, degradation of metabolite CGA42443 is not pH-dependent.</td>
</tr>
<tr>
<td>The degradation of CGA 50266 is not pH depandent.</td>
<td>The Co-RMS is not fully convinced that degradation of CGA 50266 is not pH dependent. This may be elaborated more in detail.</td>
<td>From the indicative assessment, degradation of metabolite CGA50266 in soil is not pH-dependent.
This findings is supported by the Pearson's correlation test that revealed a small negative correlation at the $p = 0.05$ significance level. The Kendall's rank correlation was not significant at the $p = 0.05$ significance level.


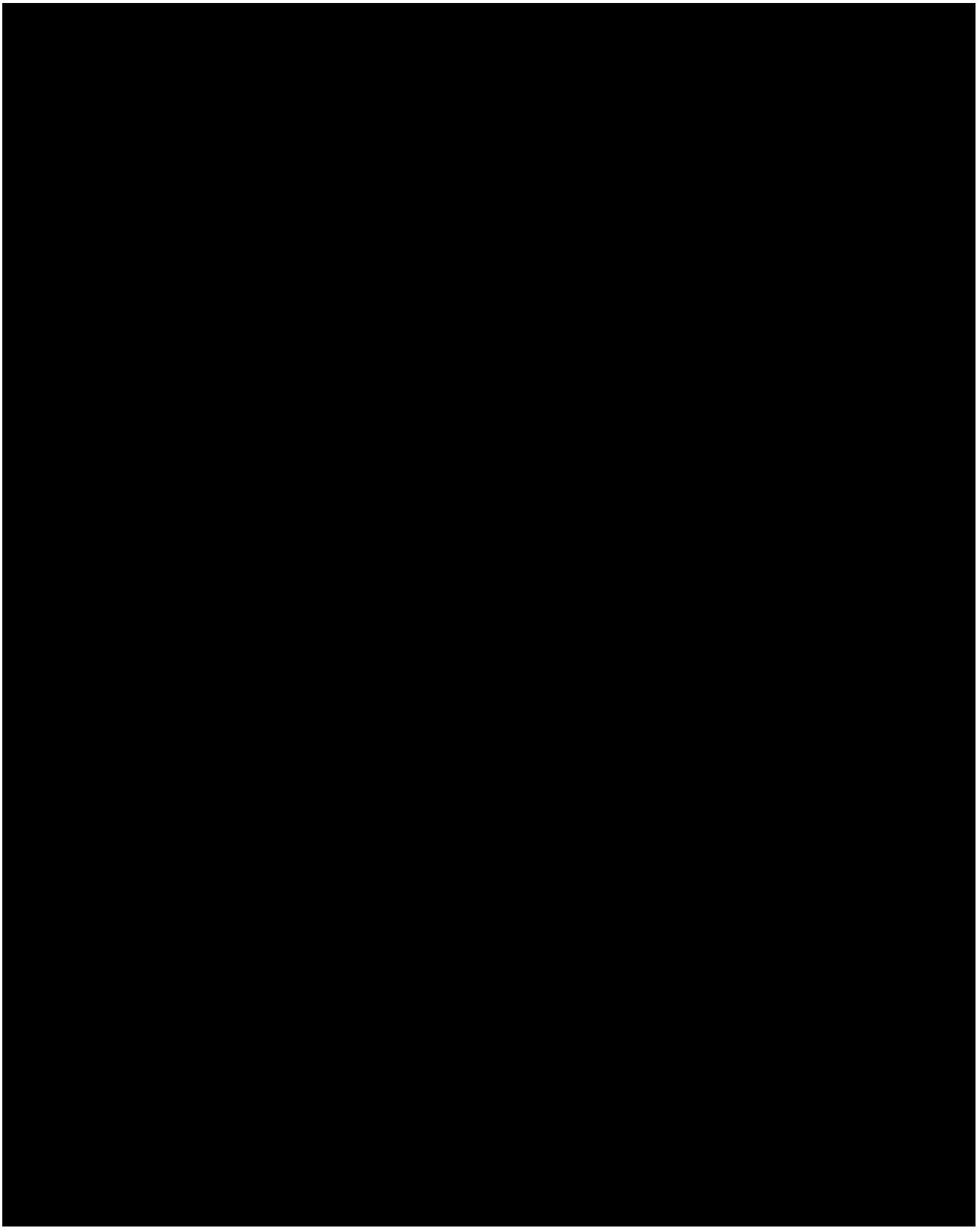
RMS HR did an own statistical analysis to evaluate correlation between degradation rates and pH value of the tested soils. Correlations among the data were tested using Pearson and Kendall's rank correlation tests and also visually.
<table>
<tr><th rowspan="2">Correlation</th><th colspan="2">Pearson's product-moment corr.</th><th colspan="2">Kendall's rank correlation test</th></tr>
<tr><th>correlation</th><th>p-value</th><th>tau</th><th>p-value</th></tr>
<tr><td>soil pH × DT_{50}</td><td>-0.512</td><td>0.299</td><td>-0.600</td><td>0.133</td></tr>
</table>
The trendline indicated that degradation of metabolite CGA50266 in soil is not pH-dependent. This findings is supported by the Pearson's correlation test and by</td>
</tr>
</table>

		the Kendall's rank correlation, they were not significant at the p = 0.05 significance level, degradation of metabolite CGA 50266 is not pH-dependent.
Position of CGA 102935 in the soil degradation scheme applied for kinetic fittings (lab and field)	The Co-RMS do not understand why CGA 102935 is considered a downstream metabolite of CGA 354742 (ESA part of the degradation pathway) but not a downstream metabolite of CGA 50266 (OXA part of the degradation pathway). Considering the structure of CGA 102935 and referring to *Simplified Degradation Pathway for Dimethachlor in Soil* (presented in part 2.8.6. of this document Volume_1) we would indeed consider CGA 102935 being a downstream metabolite in the OXA part of the degradation pathway (thus a metabolite of CGA 50266 and similar compounds).	The applicant proposed the soil degradation scheme, position of the metabolite CGA 102935 is pretty much the same from the last evaluation of the DAR. We can discuss this issue further with the Applicant, EFSA and other MS.
Position of CGA 102935 in the soil degradation scheme applied for kinetic fittings (lab and field)	The Co-RMS do not understand why CGA 102935 is considered a downstream metabolite of CGA 354742 (ESA part of the degradation pathway) but not a downstream metabolite of CGA 50266 (OXA part of the degradation pathway). Considering the structure of CGA 102935 and referring to *Simplified Degradation Pathway for Dimethachlor in Soil* (presented in part 2.8.6. of this document Volume_1) we would indeed consider CGA 102935 being a downstream metabolite in the OXA part of the degradation pathway (thus a metabolite of CGA 50266 and similar compounds).	The applicant proposed the soil degradation scheme, position of the metabolite CGA 102935 is pretty much the same from the last evaluation of the DAR. We can discuss this issue further with the Applicant, EFSA and other MS.
CGA369873 – A laboratory study to determine the sublethal	A NOEC of 29.42 mg/kg dw soil is proposed. At the concentration determined	NOEC value of 1000 mg test item / kg was determined. No clear dose response was achieved, reduction in fecundity at six highest doses, but they

effects on the Earthworm *Eisenia fetida* (Annelida: Oligochaeta)	to be NOEC a reduction of 13.17 % was recorded that was not significant when compared to control.	were not statisticaly significant when compared to control.
CGA354742 - A Laboratory Study to Determine the Acute and Sublethal Effects on the Collembolan *Folsomia candida* (Arthropleona: Isotomidae)	A NOEC of 52.94 mg/kg dw soil is suggested. At the concentration determined to be NOEC a reduction of 28 % was recorded that was not significant when compared to control.	NOEC value of 1000 mg test item / kg was determined. No clear dose response was achieved. Reduction in fecundity of 28% at the NOEC dose was recorded but at the lower dose, 95.28 mg test item / kg reduction of 21.33 % was also recorded. Recorded reductions were not statisticaly significant when compared to control.
CGA369873 - A Laboratory Study to Determine the Acute and Sublethal Effects on the Collembolan *Folsomia candida* (Arthropleona: Isotomidae)	A NOEC of 52.94 mg/kg dw soil is suggested. At the concentration determined to be NOEC a reduction of 28 % was recorded that was not significant when compared to control.	NOEC value of 1000 mg test item / kg was determined. No clear dose response was achieved. Reduction in fecundity of 28% at the NOEC dose was recorded but at the lower dose, 95.28 mg test item / kg reduction of 27 % was also recorded. At the dose that of 308.7 mg test item / kg an increase of 8.7 % was recorded. Recorded reductions were not statisticaly significant when compared to control.
CGA369873 - A Laboratory Study to Determine the Acute and Sublethal Effects on the Collembolan *Folsomia candida* (Arthropleona: Isotomidae)	A NOEC of 29.42 mg/kg dw soil is suggested. At the concentration determined to be NOEC a reduction of 30.25 % was recorded that was not significant when compared to control. At higher test concentrations reductions between 19 % and 37 % were observed.	NOEC value of 555.6 mg test item / kg was determined. No clear dose response was achieved. Reduction in fecundity of 30 % at the NOEC dose was recorded but at the lower doses, even larger reductions of fecundity were recorded.
SYN530561 - A Laboratory Study to Determine the Acute and Sublethal Effects on the Collembolan *Folsomia candida* (Arthropleona: Isotomidae)	A NOEC of 171.5 mg/kg dw soil is proposed by the co-RMS. At the three highest test concentrations a reduction in fecundity of 12, 22 and 40 % was observed.	RMS agrees that 40.78 % reduction determined at the NOEC value of 1000 mg/kg is to large and that the NOEC value should be lower. RMS proposed the NOEC of 555.6 mg test item / kg. At this concentration reduction of 22.84 % was recorded, but it was not statistical different compared to the control.
CGA354742 - A Laboratory Study to Determine the Acute and Sublethal Effects on the Predatory Mite *Hypoaspis aculeifer* (Acari: Laelapidae)	A NOEC of 95.28 mg/kg dw soil is suggested. At the concentration determined to be NOEC a reduction of 21 % was recorded that was not significant when compared to control.	RMS does not agree with the proposed reduction of the NOEC value. The NOEC was determined to be 171.5 mg test item/kg dry soil.
SYN530561 - A Laboratory Study to Determine the Acute	A NOEC of 95.28 mg/kg dw soil is suggested. At the concentration determined	RMS does not agree with the proposed reduction of the NOEC value. The NOEC was determined to be

and Sublethal Effects on the Predatory Mite *Hypoaspis aculeifer* (Acari: Laelapidae)	to be NOEC a reduction of 23.9 % was recorded that was not significant when compared to control.	171.5 mg test item/kg dry soil.

3.2 PROPOSED DECISION



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3.4 APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

General

Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances.
Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products.

Section identity, physical chemical and analytical methods

Section physico chemical properties

ECHA (2017). Guidance on the Application of the CLP Criteria 2017 vers 5.0
UN recommendations on the Transport of Dangerous Goods (2015). Manual of tests and criteria Annex 6 2015 rev 6

Section analytical methods

Volume 3CA – B5: analytical methods
Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414 (SANCO/3029/99 rev. 4)
Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414 (SANCO/3030/99 rev. 4)
Guidance document on pesticide residue analytical methods
(SANCO/825/00 rev. 8.1)

Section Data on application and efficacy

SANCO/2012/11251 rev. 4 (2014) Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (the Renewal Regulation).

Section Toxicology

ECHA (European Chemicals Agency), 2015: Guidance on the Application of the CLP Criteria; Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Version 4.1
EFSA (European Food Safety Authority), 2017. Guidance on Dermal Absorption. EFSA Journal 017;15(6):4873
European Commission, 2009. Guidance documenton the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009.
EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, 2014. EFSA Journal 2014;12(10):3874.
EFSA Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009, 2019. EFSA Journal 2018;16(6):5311.
European Commission, 2001. Guidance for the setting of an acute reference dose (ARfD). 7199/VI/99 rev 5. Dated 5 July 2001.
European Commission, 2003. Guidance Document on Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC. SANCO/221/2000-rev. 10 - final, 25 February 2003.
European Commission, 2006. Draft Guidance for the setting and application of acceptable operator exposure levels (AOELs) SANCO/7531, 7 July 2006 rev.10

Section Residue and consumer risk assessment

OECD Guidance Document on the Definition of Residue ENV/JM/MONO(2009)30

OECD Guidelines for the Testing of Chemicals 506. Stability of Pesticide Residues in Stored commodities. (16 October 2007).
OECD Guidelines for the Testing of Chemicals 501. Metabolism in crops. (8 January 2007).
OECD Guideline for the Testing of Chemicals, Metabolism in Rotational Crops, Guideline 502, January 2007.
Commission of the European Communities, Testing of Plant Protection Products in Rotational Crops; 7524/VI/95 (rev. 2).
OECD Test Guideline 504: Residues in rotational crops (limited field studies), (8 January 2007).
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