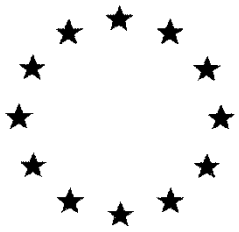
European Commission



Draft Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009

Napropamide-M

Volume 1

Rapporteur Member State: United Kingdom

Version History

When	What
June 2017	Initial DAR

Table of contents

Level 1

Napropamide-M

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 Assessment Report has been prepared to evaluate the dossier for the new active substance napropamide-M, and its formulated product D-Devrinol. The dossier was submitted for the first active approval under Regulation (EC) No 1107/2009, with the United Kingdom carrying out the assessment as the Rapporteur Member State.

The active substance is a herbicide for the control of annual grasses and broad-leaved weeds. This dossier contains data and information to support a limited range of representative uses of the active substance for which it is intended to demonstrate that, for one preparation, the requirements of Regulation (EC) No 1107/2009, Article 4 can be met.

The representative formulation, D-Devrinol, is a suspension concentrate containing 450 g active substance/L. The representative uses for D-Devrinol are winter oilseed rape, and brassica vegetable crops. These uses are intended to include the proposed major commercial applications, and represent exposure scenarios sufficiently rigorous to allow adequate evaluation of risk to humans and the environment.

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

The UK, acting as the Rapporteur Member State (RMS), evaluated the dossier and produced a Draft Assessment Report (DAR). No Co-RMS was assigned to this evaluation.

1.1.3. EU Regulatory history for use in Plant Protection Products

Napropamide-M is a new active substance and products containing it have not been previously authorised in the EU. It is the resolved single isomer version of racemic napropamide which has been established on the market in plant protection products for a number of years.

1.1.4. Evaluations carried out under other regulatory contexts

Napopamide-M is a new active substance with herbicidal action. This dossier is the application of UPL Europe Ltd for the first approval of napropamide-M in accordance with Regulation (EC) No. 1107/2009. No registrations or authorisations of napropamide-M containing plant protection products are existent in EU Member States or elsewhere. Currently there are also no other relevant EU-evaluations of the active substance carried out in the framework of other relevant EU-legislation (e.g. biocides, flavourings, food additives, cosmetics).

There are currently no JMPR evaluations published for napropamide-M.

There is currently no harmonised classification for napropamide-M in accordance with 1272/2008.

1.2. APPLICANT INFORMATION

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

Name: UPL Europe Ltd

Address:	The Centre, 1st Floor Birchwood Park Warrington WA3 6YN United Kingdom
Contact:	[redacted]
Telephone No.:	[redacted]
E-mail:	[redacted]
Telefax No.:	[redacted]

1.2.2. Producer or producers of the active substance

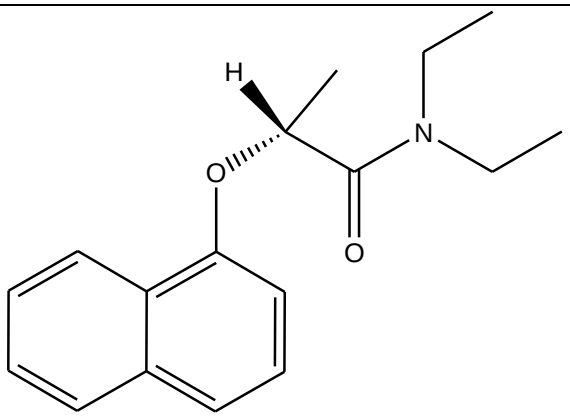
Name:	UPL Limited
Address:	Uniphos House 11th Road Madhu Park Khar (West) 40052 Mumbai India
Contact:	[redacted]
Telephone No.:	[redacted]
E-mail	[redacted]

1.2.3. Information relating to the collective provision of dossiers

This application is submitted for the first approval of napropamide-M in accordance with Article 7 of Regulation (EU) No. 1107/2009. UPL Europe Ltd, is the only applicant and owner of a complete data package regarding the new active substance napropamide-M (including old napropamide studies). The formation of task forces is not applicable to this evaluation.

1.3. IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1. Common name proposed or ISO-accepted and synonyms	Napropamide-M ISO 1750 (provisionally approved) Synonyms: D-napropamide
1.3.2. Chemical name (IUPAC and CA nomenclature)	
IUPAC	(*R*)-(-)-*N*,*N*-diethyl-2-(1-naphthyloxy)propionamide
CA	(-)-*N*,*N*-diethyl-2-(1-naphthalenyloxy)propanamide
1.3.3. Producer's development code number	HBW07
1.3.4. CAS, EEC and CIPAC numbers	
CAS	41643-35-0
EEC	Not assigned
CIPAC	976 (assigned by CIPAC January 2015)
1.3.5. Molecular and structural formula, molecular mass	
Molecular formula	$C_{17}H_{21}NO_2$

Structural formula	
Molecular mass	271.35
1.3.6. Method of manufacture (synthesis pathway) of the active substance	Confidential. Please refer to Volume 4 Annex C.
1.3.7. Specification of purity of the active substance in g/kg	Minimum purity – napropamide-M (D-isomer): > 930 g/kg Minimum purity – active substance of napropamide-M (based on sum of L and D-isomer): ≥ 965 g/kg
1.3.8. Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1. *Additives*	Confidential. Please refer to Volume 4 Annex C.
1.3.8.2. *Significant impurities*	Confidential. Please refer to Volume 4 Annex C.
1.3.8.3. *Relevant impurities*	None
1.3.9. Analytical profile of batches	Confidential. Please refer to Volume 4 Annex C.

1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1. Applicant	UPL Europe Ltd
1.4.2. Producer of the plant protection product	UPL Europe Ltd
1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product	D-Devrinol Development code No.: HBW03 (representative formulation) HBW01 (development formulation)* * HBW01 only used in efficacy testing
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**	Confidential. Please refer to Volume 4 Annex C. Content of pure active substance: 450 g/L[1] or 41.3% w/w[2] Content of technical active substance:[1] 466 g/L or 42.8 % w/w[2] 1 - at a typical purity of the technical active substance of 96.5% (sum of D-isomer plus L-isomer). 2 - Using relative density D^{20}_4 = 1.09
1.4.4.2. **Information on the active substances**	Contains 450g napropamide-M/L Please refer to Section 1.3 above
1.4.4.3. **Information on safeners, synergists and co-formulants**	Confidential. Please refer to Volume 4 Annex C.
1.4.5. Type and code of the plant protection product	Suspension concentrate (SC)
1.4.6. Function	Herbicide
1.4.7. Field of use envisaged	Weed control in agriculture and horticulture. For use on winter oilseed rape and vegetable brassicas.
1.4.8. Effects on harmful organisms	Herbicide on weeds in a range of broad-leaved crops that works by root uptake with acropetal translocation and selective, systemic activity. It is classified in HRAC Group K3 – Inhibition of cell division/WSSA Group 15.

1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT

The intended use for napropamide-M is as an agricultural/horticultural herbicide treatment on winter oilseed rape and vegetable brassicas, for the control of annual grasses and broad-leaved weeds.

Refer to table 1.5.1 below for more detail of representative uses.

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) (l)	Remarks (m)
					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)	Water l/ha min max	Lk a.i./ha min max (*) (g/ha)		
Winter oilseed rape	All zones	HBW03	F	Annual grasses and broad-leaved weeds	SC	450 g/L	Broadcast soil spray and incorporation	Pre-sowing, summer-autumn	1	na	0.255-0.3825	200-300	0.765	na	
Winter oilseed rape	All zones	HBW03	F	Annual grasses and broad-leaved weeds	SC	450 g/L	Broadcast soil spray only, no incorporation	Pre-sowing, summer-autumn	1	na	0.255-0.3825	200-300	0.765	na	
Brassica vegetable crops	All zones	HBW03	F	Annual grasses and broad-leaved weeds	SC	450 g/L	Broadcast soil spray and incorporation	Pre-planting / pre-sowing, spring-summer	1	na	0.1275-0.3825	200-600	0.765	na	Treatment is made to soil prior to sowing or transplanting of crops
Brassica vegetable crops	All zones	HBW03	F	Annual grasses and broad-leaved weeds	SC	450 g/L	Broadcast soil spray only, no incorporation	Pre-planting / pre-sowing, spring-summer	1	na	0.1275-0.3825	200-600	0.765	na	Treatment is made to soil prior to sowing or transplanting of crops
Winter oilseed rape	All zones	HBW03	F	Annual grasses and broad-leaved weeds	SC	450 g/L	Broadcast soil spray only, no incorporation	Post-sowing, pre-emergence / BBCH 00-08, summer-autumn	1	na	0.255-0.3825	200-300	0.765	na	
Brassica vegetable crops	All zones	HBW03	F	Annual grasses and broad-leaved weeds	SC	450 g/L	Broadcast soil spray only, no incorporation	Post-sowing, pre-emergence / BBCH 00-08, spring-summer	1	na	0.1275-0.3825	200-600	0.765	na	Treatment is made to soil post-sowing but not post-transplanting of crops

* For uses where the column „Remarks“ in marked in grey further consideration is necessary. Uses should be crossed out when the applicant no longer supports this use(s).
(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 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 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

Note: Brassica vegetable crops covered by the GAP include (According to Commission Regulation (EU) No 212/2013 of 11 March 2013 replacing Annex I to Regulation (EC) No 396/2005): Broccoli (calabrese, Broccoli raab, Chinese broccoli), cauliflower, brussels sprout, Head cabbage (pointed head cabbage, red cabbage, savoy cabbage, white cabbage) Chinese cabbage (Indian or Chinese) mustard, pak choi, Chinese flat cabbage/ai goo choi), choi sum, Peking cabbage/pe-tsa) kale (Borecole/curly kale, collards, Portuguese Kale, Portuguese cabbage, cow cabbage) and kohl rabi. *Note the kale, chinese cabbage and kohl rabi uses are not currently supported by residue data.

1.5.2. Further information on representative uses

D-Devrinol is a formulated suspension concentrate (SC) product containing 450g napropamide-M/L. The maximum rate for the product is 1.7 L product/ha.

The method of application is as a Broadcast soil spray, with or without incorporation. Where no incorporation is planned, or before or after drilling of the seed, it is applied directly to the soil surface using a conventional broadcast sprayer. Seeds should be drilled to a minimum 50 mm depth and seedbeds must have a fine, firm tilth. Where incorporation is planned, incorporation should occur within 24 hours of application.

As D-Devrinol 450 g/L SC is applied to bare soil as a pre-sowing or pre-emergent herbicide, a PHI is not applicable for winter oilseed rape or brassica vegetables. Only supported uses, including brassica vegetable crops and winter oilseed rape, may be drilled/transplanted as following crops. Crops may be drilled only in the following planting season of the next calendar year.

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

No other uses are applied for to support the setting of MRLs for uses beyond the representative uses.

1.5.4. Overview on authorisations in EU Member States

Not applicable (napropamide-M is a new active substance not previously authorised in the EU).

Napropamide-M is the resolved single isomer version of racemic napropamide which has been established on the market in plant protection products for a number of years. Napropamide was a List 3A review herbicide substance under Directive 91/414/EEC but was voted for non inclusion in Annex I in 2008. Following a resubmission application by the applicant, an amending Directive for the Annex I inclusion for napropamide (Commission Directive 2010/83/EU) was voted, and napropamide was approved with an entry into force date of 1st January 2011.

Level 2

Napropamide-M

2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

2.1. IDENTITY

Napropamide-M is a new active substance which acts as a pre-emergence herbicide to control annual grasses and broad-leaved weeds in winter oilseed rape and brassica vegetable crops. It is a herbicide belonging to the group of cell division inhibitors via inhibition of very long chain fatty acid (VLCFA) synthesis (HRAC Group K3).

Acceptable information has been provided by the applicant regarding the identity of napropamide-M and the representative product D-Devrinol.

2.2. PHYSICAL AND CHEMICAL PROPERTIES

2.2.1. Summary of physical and chemical properties of the active substance

The pure active substance, napropamide-M, has a melting point of 92.2ºC and boiling point of 319.4ºC. Its vapour pressure (3.8 x 10^{-6} Pa at 25ºC) and volatility (Henry's low constant: 2.644 x 10^{-5} $Pa.m^3$ mol^{-1} at 20ºC) are very low. The water solubility of the active is 0.039 g/L and this is not expected to be pH dependent as napropamide-M does not dissociate. The log Pow of napropamide-M is 3.27 as determined at pH 7. Napropamide-M is not flammable or explosive and does not have oxidising properties in accordance with the CLP regulation.

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

The product D-Devrinol 450 g/L SC (HBW03) is a suspension concentrate formulation. The appearance of the product is a creamy beige coloured liquid. It is not concluded to be explosive and has no oxidising properties. It has no self-ignition temperature when tested up to >400°C. The product is not considered to be flammable. In aqueous solution it has a pH of 8.2. The formulation was found to be stable under low temperature (7 days at 0 °C), accelerated (2 weeks at 54 °C), and ambient temperature storage conditions. The stability data indicate a shelf life of 2 years at ambient temperature.

2.3. DATA ON APPLICATION AND EFFICACY

2.3.1. Summary of effectiveness

Effectiveness was assessed in 46 trials conducted in winter oilseed from 2008 to 2010. The trials were undertaken by Officially Recognised Organisations, all of which follow EPPO guidelines. Trials were conducted in Germany (2), Northern France (5), Southern France (4), UK (2), Poland (10), Spain (12), Italy (10) and Greece (1). Therefore trials were conducted in the Maritime, North East and Mediterranean EPPO zones.

No effectiveness data were available from use in vegetable brassicas. However, the uses are identical in terms of dose rate and method of application and therefore within the risk envelope. Further consideration of the scope to extrapolate from oilseed rape to vegetable brassicas will need to be considered by MS at product authorisation.

The results show that generally Blackgrass (ALOMY), Loose silky bent (APESV) and Common poppy (PAPRH) are susceptible, whilst Fat hen (CHEAL), Mayweeds (MATSS), Cleavers (GALAP) and Speedwells (VERSS) are susceptible/moderately susceptible, with some variations between zones and application timings. No trials on ALOMY were conducted in the Central zone and control may vary from that in the Southern zone. In addition, for product authorisation, additional results will be required in line with EPPO PP1/226 'Number of efficacy trials' depending on whether species are major or minor.

Overall, there is evidence that the proposed dose would be "sufficiently effective" and that the supported GAP is representative.

Refer to Section B.3.9 in Volume 3CP.

2.3.2. Summary of information on the development of resistance

Napropamide-M belongs to the chemical family of acetamides which are mitosis inhibitors. The Herbicide Resistance Action Committee (HRAC) classifies the active substance in mode of action group K3 – inhibition of cell division via inhibition of very long chain fatty acid (VLCFA) synthesis. It is the resolved single isomer version of racemic napropamide which has been established on the market in plant protection products for a number of years. Resistance to Group K3 herbicides globally has been reported in 5 weed species. One case has been reported in Europe in ALOMY although this was not resistance specifically to napropamide. This highlights the importance of submission of effectiveness data on ALOMY in the Maritime zone at product authorisation stage.

Refer to Section B.3.10 in Volume 3CP.

2.3.3. Summary of adverse effects on treated crops

The proposed crops are stated as Winter oilseed rape (BRSNW), Cabbage (BRSOL), Cauliflower (BRSOB), Brussel sprouts (BRFOF) and Calabrese/Broccoli (BRSOK).

Crop safety was assessed in the 46 effectiveness trials and in 14 specific crop safety trials in winter oilseed rape. Trials were conducted in Germany (2), Northern France (1), Southern France (1), UK (2), Poland (4), Spain (2) and Italy (2). Trials included doses up to 2.16 kg/ha (2.8N). Phytotoxicity was recorded in 2 effectiveness trials. In both these trials (S08-02687-04 and OGL-11-8341-FR02), the phytotoxicity reported did not exceed 5%. In the other 58 trials (including all selectivity trials), no phytotoxicity was reported.

No data have been submitted to support use on brassica vegetable crops. However, the uses are identical in terms of dose rate and method of application. Further consideration of the scope to extrapolate from oilseed rape to vegetable brassicas will need to be considered by MS at product authorisation.

The submitted data support crop safety in winter oilseed rape. Further information to support the use of D-Devrinol 'HBW03' in terms of crop safety and selectivity will be required and considered at product authorisation.

Refer to Section B.3.11 in Volume 3CP.

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

In terms of risks to succeeding crops the applicant in a draft label has included the following wording:

Only supported uses, including brassica vegetable crops and winter oilseed rape, may be drilled/transplanted as following crops. Crops may be drilled only in the following planting season of the next calendar year.

The RMS concluded that this is supported by the data presented. The details of succeeding crops which may be planted following crop failure and subsequent to a normal harvest will be considered at product evaluation stage.

The information submitted for risks to adjacent crops indicates that at the proposed dose rate of 765 g napropamide-M will be within acceptable parameters for all adjacent crops. It is therefore considered that napropamide-M can be authorised for used on the proposed crops without any restrictions relating to adjacent crops.

Refer to Section B.3.12 in Volume 3 CP.

2.4. FURTHER INFORMATION

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

Acceptable information has been provided to address these points. Refer to Volume 3 CA and CP, Section B.4.

2.4.2. Summary of procedures for destruction or decontamination

Acceptable information has been provided to address these points. Refer to Volume 3 CA and CP, Section B.4.

2.4.3. Summary of emergency measures in case of an accident

Acceptable information has been provided to address these points. Refer to Volume 3 CA and CP, Section B.4.

2.5. METHODS OF ANALYSIS

2.5.1. Methods used for the generation of pre-authorisation data

Technical material

Acceptable methods were available to support the analysis of the active substance (Napropamide-M) within the technical material, and to distinguish between Napropamide-M and the L-isomer of napropamide. Methods were also available for the determination of other impurities within the technical material. Details of these methods are described within the Volume 4 document due to the commercial sensitivity of this information.

Methods were provided to analyse the active content within water and octanol at levels appropriate to support the generation of the K_{OW} for the active (Napromamide-M) and metabolites (Naphthalen-1-ol (Alpha-Naphthol), 2-(1-naphthyloxy) propanoic acid [NOPA], N,N-diethyl-2(4-hydroxy-1-naphthyl)propanamide (napropamide isomer I) and N,N-diethyl-2(1-hydroxy-2-naphthyl)propanamide (Napropamide isomer II)). The majority of these methods were considered to be fit to support the data generation phase, however for 'Napropamide isomer II', the method was not considered to be sufficiently validated, due to low recoveries (27.1 – 27.5%) for the octanol phase . However, it is noted that the validation data obtained for Napropamide isomer II were precise (even though the accuracy was poor), so the method could be used to estimate the likely content within the octanol phase, provided that the low recoveries are taken into account. It should be noted that low precision was evident for Napropamide isomer II in the octanol saturated water (%RSD = 30.1, recoveries = 44.2 – 108.0% (n = 5)). These validation data lie outside of the criteria indication within the SANCO 3030/99 rev 4 guidance.

Plant protection product

A suitable validated method to determine the active substance within the formulated product (to support the storage stability study) was available; the isomer ratio (D-isomer: L-isomer) was determined in the formulation using chiral column by determination of relative peak areas. A validated method was also provided for the specific determination of the D-isomer (using chiral methodology) in the formulation. These methods would be also be suitable for monitoring.

Methods supporting the Mammalian Toxicology risk assessment

Study	Matrix	Method	LOQ	Acceptability
(Report No. 228-2-13-6178 with Amended Final Report) – Raithatha, 2015	Test diet	HPLC-UV (at 230 nm)	1000 mg/kg	The method has been satisfactorily validated.
(Report No. 228-2-13-7271) – Raithatha, 2013	Test diet	HPLC-UV (at 230 nm)	600 mg/kg	The method has been satisfactorily validated.
(Report No. 228-2-14-7333) – Sriram, 2014	Rat Plasma	LC-MS/MS	50 ng/mL	The method has been satisfactorily validated.

Study	Matrix	Method	LOQ	Acceptability
(Report No. RRC-79-26) – Katague, 1979	-	-	-	Only minimal validation data have been provided, which are insufficient to confirm whether this method is fit for purpose. Data gap for further validation data.
(Report No. EHC-88-11) – Earley, 1988	Rodent test diet	HPLC-UV (at 290 nm)	2.36 mg/kg	The method is considered to be fit for its intended analytical application.
(Report No. EHC-89-7) – Mays, 1989	Rodent test diet	GC-NPD	4.0 mg/kg	Further information regarding the test protocol is required to conclude on the acceptability of the method. Data gap for further validation data.
(Report No. D03526) – Pothmann, 2011	-	-	-	There are insufficient validation data to confirm the acceptability of the method. Data gap for further validation data.

Methods supporting the Residues risk assessment

Study	Matrix	Method	LOQ	Acceptability
(Report No. AU-2012-62) – Li, 2013	Cabbage, strawberry, dry beans and canola seeds	LC-MS/MS	0.01 mg/kg	The method has been satisfactorily validated.
(Study No: OA00567) – Norris, 2002	Brussels sprouts, cauliflower and cabbage	GC-NPD	0.1 mg/kg	The method has been satisfactorily validated in accordance with SANCO/3029/99 rev.4, however it should be noted that this method does not distinguish between the D and L isomeric forms of napropamide (racemate) and only provided the concentration of the total napropamide (racemate) within brassica commodities. This has been taken into account during the evaluation of the residues field trials.
Method ARAM177 – Pay, 1990b	Oilseed rape	GC-NPD	0.05 mg/kg	While it is appreciated that the method has not been satisfactorily validated in accordance with SANCO/3029/99 rev.4, there is sufficient information to confirm that the method is fit for purpose and the pre-registration data generated using this method may be relied upon.
Method Napropamide/Crops/DB/00/1 (based on ARAM 177)	Oilseed rape	GC-NPD	-	The method is based on ARAM 177. No additional validation data have been provided with the exception of procedural recoveries. Supplementary validation data was however provided within report KB98WY (Harper, 2017c).

Study	Matrix	Method	LOQ	Acceptability
(Study No: KB98WY)' – Harper, 2017c	Wheat (whole plant, straw and grain)	GC-NPD	0.01 mg/kg	Acceptable validation data were provided (generated in line with SANCO/3029/99 rev.4) to support the method.
(Study No: RRC-83-68)' – Schwab, 1983	Various	GC-NPD	-	Insufficient validation data are available to comment on whether the method is fit for purpose. Supplementary validation data was however provided within report XD94TP (Harper, 2017a).
(Report No.: AS/5631/US) – Clark, 2002a	Tomatoes	GC-NPD	-	The methodology is based on RRC-83-68 and suffers from the same deficiencies - insufficient validation data. Supplementary validation data was however provided within report XD94TP.
(Report No.: 20044048/I1-FPCF) – Balluff, 2005b	Cabbage and cauliflower	LC-MS/MS	0.01 mg/kg	While the method validation does not strictly comply with the requirements set within the SANCO/3029/99 rev.4 guidance, the method may be considered to be fit for its intended purpose. The residues data generated using this method can be relied upon for risk assessment purposes.
(Report No.: XD94TP) – Harper, 2017a	Cabbage	GC-NPD	0.01 mg/kg	Acceptable validation data were provided (generated in line with SANCO/3029/99 rev.4) to support the method.

Methods supporting the Fate and Behaviour risk assessment

Study	Matrix	Method	LOQ	Acceptability
(Report No. S10-00191) – Weir, 2010	Soil	LC-MS/MS	0.001 mg/kg (Napropamide, racemate) 0.005 mg/kg (2-naphtoxypropionic acid)	The method was satisfactorily validated in accordance with SANCO/3029/99 rev.4 for both analytes.
(Report No. ARAM 178) - J. Pay, 1990a	Soil	GC-NPD	0.1 mg/kg Napropamide (racemate)	The method has not been strictly validated in accordance with SANCO/3029/99 rev.4, the results do give some assurance that the method is fit for data generation purposes and it is considered that data generated using this methodology may be relied upon for risk assessment.
(Report No. BH69LF) – Harper, 2017b	Soil	GC-NPD	0.01 mg/kg	Acceptable validation data were provided (generated in line with SANCO/3029/99 rev.4) to support the method.

Methods supporting the Ecotoxicology risk assessment

Study	Matrix	Method	LOQ	Acceptability
(Report No 228-2-13-6179) – Naik, 2013	Reconstituted water Alga media	HPLC-UV (220 nm)	0.01 mg/L 0.01 mg/L	The method has been validated in accordance with EU guidance document SANCO/3029/99 rev. 4. Isomer ratio and hence optical purity can be determined using a qualitative chiral assay. However, it is noted that a confirmatory method has not been provided.
(Report No 123-153) – Foster, 1990	Avian test diet	GC-NPD	497 mg/kg	While the method has not been satisfactorily validated in accordance with SANCO/3029/99 rev.4, it may be regarded as fit for its intended analytical purpose as a data generation method.
(Report No D03458) – Liedtke, 2011	Spiked Test Water Samples	HPLC-UV (280 nm)	7.8 mg/kg	The method has not been satisfactory validated in accordance with SANCO/3029/99 rev. 4. However, the method may be regarded as fit for purpose and it provides some measure of assurance with respect to the acceptability of the toxicological data generated in Report No D03458.
(Report No UPH021/013213) – Jenkins, 2002a	SIS Lemna dilution medium Jawarski's algal medium	GC-FID	5.24 mg/L 120 mg/L	The method has not been strictly validated in accordance with SANCO/3029/99 rev.4, however the validation data does provide some confidence in the ability of the method to detect napropamide (racemate) within these two matrix types. While the method validation data do not strictly comply with the requirements of the guidance, they may be considered supportive of the risk assessment data generated using this method and present within the study report.
(Project No 98011215) – Hermes and Wydra, 2015	Overlying water Sediment	HPLC-UV (220 nm)	0.1 mg/L 0.2 mg/kg	While the method has not been strictly validated in accordance with SANCO/3029/99 rev.4, it may be regarded as fit for its intended analytical purpose as a data generation method.
(Report No 11 10 48 017 W) – Juckeland, 2012a	Aquatic test media	HPLC-UV (235 nm) or HPLC-MS (m/z 272)	0.01 mg/L	The method for the determination of napropamide metabolite isomer-I in aquatic media was satisfactorily validated in accordance with SANCO/3029/99 rev.4

Study	Matrix	Method	LOQ	Acceptability
(Report No 11 10 48 018 W) – Juckeland, 2012b	Aquatic test media	HPLC-UV (235 nm) or HPLC-MS (m/z 272)	0.025 mg/mL	The method for the determination of napropamide metabolite isomer-II in aquatic media was satisfactorily validated in accordance with SANCO/3029/99 rev.4
(Report No. D03572) – Liedtke, 2011	Spiked test water samples	HPLC-UV (280 nm)	4.32 mg/mL	While the method has not been strictly validated in accordance with the SANCO/3029/99 rev.4 guidance, the method was considered to be fit for purpose.
(Report No. 228-2-13-6185) – Amruskar, 2013	Algal media	HPLC-UV (220 nm)	0.01 mg/L	The method is satisfactorily validated in accordance with SANCO/3029/99 rev.4, though it is noted that a confirmatory method has not been provided.

2.5.2. Methods for post control and monitoring purposes

Plant protection product

Monitoring methods for the determination of napropamide-M within D-Devrinol were available:

1. HPLC-UV at 230 nm (capable of distinguishing between the napropamide-M D isomer and the L-isomer). LOQ = 34% w/w (formulation)
2. HPLC-UV at 280 nm (capable of detecting napropamide-M as the D-isomer). LOQ = 45% w/w (formulation)

Plant matrices
A method of analysis for detection of napropamide-M in plant matrices accommodating high water content (cabbage), high protein / dry commodities (dry beans), high oil content (canola seeds) and high acid content (strawberry) crops was provided. The supported LOQs are 0.01 mg/kg for each commodity.

Animal matrices
Monitoring methods for the determination of residues in animal tissues were not required as residues at harvest in commodities potentially used for animal diet were all below the default limit of quantification (0.01 mg/kg). Additionally animal metabolism studies showed that napropamide (racemate) and napropamide-M were extensively metabolised and residues in edible tissues are very low.

Soil
Methods were validated for napropamide (racemate) using GC-MS (DFG S19 multi-residue method). The method was validated to an LOQ of 0.01 mg/kg. It should be noted that while the method was capable of determining the total napropamide (racemate) content within the soil, validation data has not been provided for the individual isomers.

Water
The water monitoring methods (LC-MS/MS) were available to detect nampropamide-M in surface and drinking water. The validated LOQs 0.05 µg/L (drinking water) and 0.1 µg/L (surface water). Acceptable drinking water ILV was provided.

Air
A monitoring method for air detected (LC-UV at 215 nm) was available for the detection of napropamide (racemate) within air. The supported LOQ is 3.33 x10-3 mg/m^3.

Body fluids and tissues

It should be noted that bespoke methods were not provided to determine the napropamide-M content within bodily tissues. However, methods were available for the determination of napropamide racemate within animal tissues: GC/MS (DFG S19), LOQ = 0.02 mg/kg for milk, muscle, kidney and liver. This method was evaluated during the EU review for napropamide racemate (Demark, 2005).

Furthermore a method for the determination of napropamide-M in rat plasma was available: LC-MS/MS, with a validated LOQ of 50 ng/mL.

2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

Napropamide-M is a new active substance belonging to the chemical group of alkanamides. It is a selective systemic herbicide, absorbed by the roots and translocated acropetally. It inhibits root development and growth and is used for pre-emergence control of grasses and broad-leaved weeds in a wide range of crops.

Napropamide-M is the resolved isomer ((R)-(-)-N,N-diethyl-2-(1-naphthyloxy)propionamide) of the napropamide racemic mixture ((RS)-N,N-diethyl-2-(1-naphthyloxy)propionamide) containing the R and S isomers (also known as D and L forms, respectively) in a 1:1 ratio.

A comprehensive database on napropamide racemate was evaluated for the approval of napropamide. The EFSA Conclusion (EFSA, 2010) was published on 29/4/2010. There were no data gaps, issues that could not be finalised or critical areas of concern relating to the toxicology assessment. The approval of the active entered into force on January 1st 2011 (Commission Directive 2010/83/EU of 30 November 2010).

The applicant for napropamide (racemate) was United Phosphorus. The applicant for napropamide-M is UPL Europe Limited, previously known as United Phosphorus. The RMS for napropamide was Denmark and wherever possible the text of the napropamide DAR has been used. However, these studies were checked to determine if they were still valid and supported the original outcome. The study summaries from these old studies have, except where stated, been reproduced from the original DAR; minor editorial and formatting changes have been made as appropriate. If the original evaluations were deemed to be fit for purpose, they were not re-edited.

The following toxicology studies and additional information on napropamide-M were provided:

- ADME study in rats
- 28 day oral study in rats (dose range-finding study)
- 90 day oral study in rats
- Acute toxicity studies
- Genotoxicity studies
- Medical surveillance of manufacturing personnel

These studies are new and have not previously been evaluated; they have been submitted by the applicant in support of the approval of napropamide-M. For all other end points no new data have been submitted. All study protocols for the new studies fully followed the respective OECD test guidelines, unless stated otherwise.

On the basis that the ADME and toxicity studies on napropamide racemate will have assessed the combination of both napropamide enantiomers, the applicant has developed a strategy to bridge to the existing ADME and toxicology studies on napropamide racemate for napropamide-M. The applicant's new active substance submission includes new studies conducted on napropamide-M to support bridging to the napropamide racemate database.

In summary, a metabolism study and a 90-day toxicity study in the rat on napropamide-M, with an equivalent high dose of napropamide racemate, demonstrated that both compounds exhibited comparable metabolism and toxicological properties. In addition the results of the acute toxicity studies for napropamide-M are consistent with those of napropamide racemate and they are therefore considered to have equivalent acute toxicity. The new genotoxicity studies conducted on napropamide-M further supported the bridging approach.

The opinion of the RMS is that napropamide-M (i.e. the R isomer) and the racemate have equivalent toxicity. Therefore, where appropriate, toxicity studies conducted on napropamide racemate have been used to satisfy a number of data points for napropamide-M.

Methods of analysis

Appropriate methods of analysis for all of the studies using napropamide-M have been provided (Report No. 228-2-13-6178, Raithatha, 2015; Report No. 228-2-13-7271, Raithatha, 2013; Report No. 228-2-14-7333, Sriram, 2014). These methods were fully validated in accordance with SANCO/3030/99 rev.4 (see Volume 1 Section 2.5.1, and Volume 3 CA Section B.5). Procedural recoveries, where available, were checked and found to be acceptable. The methods of analysis using napropamide were considered valid for the approval of napropamide and have therefore been accepted.

2.6.1. Summary of absorption, distribution and excretion in mammals

Five ADME studies are available to support napropamide-M. Four of the studies were done using napropamide racemate and were previously evaluated by Denmark for the approval of napropamide. Each of the studies involved investigation (single and repeat-dose) in the rat by the oral route. The summaries of these studies have not been changed (other than minor amendments to improve readability) and the individual and overall conclusions, as presented in the EFSA Conclusion (EFSA, 2010), have not changed. Additionally, a new, single-dose oral study on napropramide-M was submitted.

The findings of the studies on napropamide racemate and napropamide-M were very similar. The RMS considers the ADME characteristics of napropamide and napropamide-M to be sufficiently similar to extend the findings of the four napropamide studies to napropamide-M; therefore, the EFSA conclusions on the ADME of napropamide (EFSA, 2010) are equally applicable to napropamide-M. .

Both substances were rapidly and extensively absorbed after oral administration. In a study with napropamide racemate in bile-duct-cannulated male rats, more than 90 % of the administered radioactivity was absorbed after oral administration. Investigations of distribution showed that napropramide racemate was present in the highest levels in blood-rich organs: the liver, spleen and kidney. Seven days after oral administration, the highest concentrations of radioactivity were present in the blood of both sexes. At the 6-hour time point, the concentrations in plasma and blood were almost the same, but at all other time points the concentrations in plasma were lower than in blood, indicating that the radioactivity in blood was associated with the cell fraction.

Both napropamide and napropamide-M were extensively metabolised. The metabolite profiles for faeces were similar to that of urine for both substances, with the metabolites being mainly glucuronide conjugates; the levels of parent compounds in urine and faeces were very low. No qualitative differences were apparent between the sexes, the dose levels (30 mg/kg bw and 300 mg/kg bw), or between single and repeat-dose animals. Elimination of radioactivity from tissues/organs was almost complete 4 days after dosing, and after 7 days tissues contained less than 0.3 % of the administered dose. The route of excretion was approximately equally split between urine and faeces, although there were slight differences depending upon the duration of exposure. The percentage of administered radioactivity excreted in urine was similar for both actives (approximately 50 – 60 %), based upon single-dose administration (non bile-duct-cannulated rats), but was slightly lower (approximately 40-50 %) after repeated-dose administration. Bile duct-cannulated rats excreted a much lower proportion of the dose in urine (mean of 15 % of the applied dose), which suggested that enterohepatic circulation is an important process in the normal excretion of napropamide racemate (and by extension, napropamide-M). The potential for bioaccumulation of both parents is considered to be low.

The applicant has not conducted comparative *in vitro* metabolism studies because no agreed test methods have been published. In accordance with SANCO/10181/2013 rev 2.1 (13 May 2013) a waiver is considered acceptable until such methods are published in the form of an update of Commission Communications 2013/C 95/01 and 2013/C 95/02.The metabolic pathways proposed for napropamide-M in the rat, N-dealkylation and aromatic ring hydroxylation with subsequent conjugation to form glucuronide and sulphate conjugates, are common metabolic steps and are likely to be conserved across species including humans. Furthermore, the extensive metabolism of napropamide-M in the rat indicates that it is a good substrate for the enzymes responsible for these metabolic pathways and it could be assumed that such rapid biotransformation and elimination via these routes reduces the likelihood of alternative pathways operating in humans.

Table 2.6.1. Summary of toxicokinetic studies

Type of study	Dose levels (mg/kg b.w.)	Animal species, strain; sex	Substance	Findings	References

Type of study	Dose levels (mg/kg b.w.)	Animal species, strain; sex	Substance	Findings	References
Metabolism of napropamide-M following oral administration in the rat	Phase 1 and 3: 30 mg/kg bw (range 29.2 - 33.3 mg/kg bw) Phase 2 and 4: 300 mg/kg bw (range 281 - 302 mg/kg bw)	Male and female Sprague-Dawley rats	^{14}C-napropamide-M and unlabelled napropamide-M	Napropamide-M was rapidly excreted and extensively metabolised at both dose levels. Excretion was approximately equally split between urine and faeces. Highest tissue concentrations, 96 hours after dosing, present in organs of metabolism and elimination: liver, kidney. Peak plasma concentration: 6 hours after dosing. Generally, systemic exposure to total radioactivity increased approximately proportionally with dose.	[redacted] 2015
Elimination (balance study) and tissue distribution (residue study) after oral administration (Single dose study)	Preconditioned with non-labelled test material 5 or 25 mg/kg bw/day for 4 days. Balance study: 30 mg/kg bw Residue study: 195 mg/kg bw Both with ^{14}C-napropamide	Male and female Simonsen Albino rats	^{14}C-napropamide and unlabelled napropamide	Approximately 98.6 % of the administered radioactivity was eliminated in urine and faeces within 96 hours; 57.5 % in the urine and 40.7 % in the faeces. No detectable radioactivity was found in the expired air. Tissues and organs contained approximately 0.41 % of the administered radioactivity 96 hours after administration. No sex difference was apparent for elimination and tissue distribution. Accumulation was not evident.	[redacted] (1970)
Elimination and tissue distribution after oral administration (Single dose study)	Single dose of either 30 or 300 mg/kg bw	Male and female Sprague-Dawley rats	^{14}C-napropamide and unlabelled napropamide	Most of the radioactivity was eliminated via urine and faeces within 72 hours after a single oral administration of 30 (about 100 %) or 300 mg ^{14}C-napropamide/kg bw (about 91-95 %). The concentration of the administered radioactivity was highest in blood and tissues at 6 hours after dosing, and the concentrations were dose dependent. The radioactivity from tissues declined gradually, and the concentration of radioactive residues in tissues/organs were low 96 hours after dosing (about 1.5 % in males and 3.0 % in females). The highest concentrations were usually found in the intestines, especially within the first 72 hours. No sex difference was evident.	[redacted] (1988)
Elimination and tissue distribution after oral administration (Repeated dose study)	Single dose of 30 mg/kg bw with radio-labelled napropamide following 14 days preconditioning with 30 mg/kg bw/day of unlabelled test material	Male and female Sprague-Dawley rats	^{14}C-napropamide and unlabelled napropamide	Fourteen days of pre-treatment of male rats with napropamide had no effect on the absorption, excretion and tissue retention of ^{14}C-napropamide. Most of the radioactivity was eliminated via urine and faeces within 72 hours after dosing: males approx. 42 % (urine) and approx. 49 % (faeces), females 48 % (urine) and 42 % (faeces). Tissues contained less than 0.3 % of the administered dose seven days after dosing. The highest concentrations were found in blood, mainly associated with the blood cells. Comparatively high concentrations of radioactivity were found in liver, spleen, thyroid (females only) and kidney. No sex difference was evident in distribution.	[redacted] (1991)

Type of study	Dose levels (mg/kg b.w.)	Animal species, strain; sex	Substance	Findings	References
Biotransform-ation in the rat	Single dose of either 30 or 300 mg/kg bw	CD-1 rats	^{14}C-napropamide and unlabelled napropamide	Napropamide was extensively metabolised and rapidly eliminated. No qualitative differences were apparent between the sexes, the dose levels, or between single and repeat-dose animals. Biliary metabolites were mainly glucuronide conjugates of hydroxylated napropamide at position 4. Approximately 15 urinary metabolites were identified. Metabolite profile for faeces was similar to that of urine.	[redacted] (1991, 1993)

2.6.2. Summary of acute toxicity

The acute toxicity of napropamide-M has been investigated by the oral, dermal and inhalation routes. Skin and eye irritation have been investigated in rabbits, whilst a local lymph node assay (LLNA) is available to inform on the substance's skin sensitisation potential.

In an acute oral study conducted to the acute toxic class method, no rats died at the single dose tested of 2000 mg/kg bw (LD_{50} > 2000 mg/kg bw). Likewise, napropamide-M was not toxic by the dermal route (LD_{50} > 2000 mg/kg bw). An acute inhalation study on napropamide-M was attempted, but an aerosol with a respirable particle size could not be generated, leading to the conclusion that, under normal production methods, the physical form of the test article made it unlikely to present an inhalation hazard. However, an acute inhalation study on napropamide racemate was available (LC_{50} of >4.8 mg/l) and has been used to conclude that napropamide-M does not require classification for acute inhalation toxicity. Therefore, napropamide-M does not meet the criteria for classification for acute toxicity or STOT-SE.

The skin and eye irritation potential of napropamide-M were investigated in rabbits. In both studies all scores were 0 for all parameters at all time-points. Therefore, napropamide-M does not meet the criteria for classification for either skin or eye irritation. The potential of napropamide-M to induce skin sensitisation was investigated in a murine local lymph node assay. Napropamide-M did not induce skin sensitisation in this study and so does not meet the criteria for classification.

The acute toxicity of napropamide-M was consistent with that of napropamide racemate presented in the EFSA conclusion for that substance (EFSA, 2010).

Table 2.6.2. Summary of acute toxicity studies

Type of study	Species	Result	Reference
Oral OECD 423 (2001)	Rat	LD_{50} >2000 mg/kg bw	CA 5.2.1/01 [redacted] (2010a)
Dermal OECD 402 (1987)	Rat	LD_{50} >2000 mg/kg bw	CA 5.2.2/01 [redacted] (2010b)
Inhalation OECD 403 (2009) OECD 403 (1981)	---[a]	---[a] >4.8 mg/l	CA 5.2.3/01 [redacted] (2011) CA 5.2.3/02 [redacted] (1989)
Skin irritation OECD 404 (2002)	Rabbit	non-irritant	CA 5.2.4/01 [redacted] (2010c)
Eye irritation OECD 405 (2002)	Rabbit	non-irritant	CA 5.2.5/01 [redacted] (2011)
Skin sensitisation (LLNA) OECD 429 (2010)	Mouse	non-sensitising	CA 5.2.6/01 [redacted] (2011)

a technically unfeasible

2.6.3. Summary of short-term toxicity

Two new short-term repeated-dose oral studies (a 28-day dose-range-finding study and a 90-day dietary toxicity study, both in the rat) were conducted on napropamide-M and were evaluated for this approval for the first time. The latter study also incorporated a group that was exposed to a high dose of napropamide racemate, to enable a direct comparison of its toxicity with that of napropamide-M and thus provide support for the bridging to the napropamide racemate toxicology database. Several other studies were available on napropamide racemate and were previously evaluated by Denmark for the approval of napropamide; these included oral studies in rats, mice and dogs and a dermal study in rats. These were of varying quality and most are now old or dose-range finding studies with only limited information. Others were well conducted, more recent and guideline-compliant studies.

In the new 28-day range finding study with napropamide-M, doses of up to 10 000 ppm (849 or 971 mg/kg bw/d for male and female rats, respectively) were administered in the diet. In the new 90-day study, rats received doses of up to 10 000 ppm (872 mg/kg bw/day) of napropamide-M and 10 000 ppm (843 mg/kg bw/day) napropamide racemate in the diet. The observed toxic effects included reductions in mean body weight, increased relative kidney weights (males in the 5000 and 10 000 ppm dose group and females in the 10 000 ppm) and significant increases in relative weights of the spleen (only males in the 10 000 ppm dose group) and liver. Based on the limited information in the study (no clinical chemistry or histopathological examination) kidney, spleen and liver are potentially the target organs

The kidneys and blood system (with compensatory responses in the spleen) were identified as the target organs following dietary administration of napropamide-M and napropamide racemate at doses up to 10 000 ppm for up to 90 days. Besides increased kidney and spleen weights, histopathological changes were noted at this dose (kidney in males: regenerative/basophilic tubules, cortex and spleen in males: extra medullary haematopoiesis, EMH). From the mid-dose group (2500 ppm; 90-day study), the erythrocyte count (and associated changes in derived red cell parameters) was lowered and appeared to be associated with changes in derived red cell parameters; the primary toxic effect on the blood system therefore appears to be on red blood cells, with compensatory effects on the spleen. The NOAEL from the 90-day study was 600 ppm (equivalent to 46 mg/kg bw/day for males and 50 mg/kg bw/day for females).

In the studies on napropamide racemate using dosing periods of 4 to 6 weeks, effects were seen from doses of approximately 500 mg/kg bw/day and included decreased body weight and increased relative and/or liver weights. In rats, mild anaemia was seen, while dogs had decreased food consumptions at the highest doses. In the 90-day rat study on napropamide racemate the doses used were too low since no adverse effects were seen in the highest dose (50 mg/kg bw/day).The picture of decreased food consumption, decreased body weights and

increased liver weights, with occasional changes in liver enzymes, was also predominant in the dog in the 90-day study and in the two 1-year studies with napropamide racemate. No adverse findings were seen at gross pathology or at histopathology. The NOAELs in these studies varied from 40 to 70 mg/kg bw/day across the studies.

The dermal short-term toxicity of napropamide racemate was investigated in a 4-week study in rats conducted in accordance with GLP and OECD guidance. The study showed no treatment-related effects at any dose level. A NOAEL of 1000 mg/kg bw/day, the highest dose tested, was therefore set for systemic as well as local effects from this study.

Given the similarity of the adverse effects and the doses at which they occurred, with NOAELS in the range of 40 to 70 mg/kg bw/d for both substances in 90-day studies, the RMS concludes that the toxicological profile of napropamide-M is similar to that of napropamide racemate and it is therefore acceptable to bridge from the napropamide racemate toxicology database to meet the data requirements for napropamide-M. The conclusions drawn on the basis of all of the short term studies on napropamide racemate, as described in the EFSA Conclusion (EFSA, 2010), can thus be applied to napropamide-M.

The results of these short-term studies indicate that there are no severe or significant toxic effects at doses below the guidance cut-off values given in Regulation 1272/2008 and therefore napropamide-M does not meet the criteria for classification for repeated dose toxicity. Furthermore, in the chronic / carcinogenicity studies, the only adverse effects observed (reductions in body weights and food consumption) occurred at doses that were far in excess of the adjusted guidance cut-off values for classification in STOT-RE category 2. There is therefore consistent evidence from all the repeated-dose toxicity studies that napropamide-M does not meet the criteria for classification for STOT-RE.

Table 2.6.3. Summary of short-term studies

Type of study	Species	Dose levels tested mg/kg bw/day	NOAEL	LOAEL	Findings	Reference
Range finding oral, dietary, 28 day	RccHan: WIST strain rats	**Napropamide-M** 0, 82.9/100, 410/484, 849/971 mg/kg bw/day in males and females, respectively.	None set as range-finding study.	Effects seen from 410/484 mg/kg bw/day in males and females, respectively.	Decreased bw. Increased relative kidney weights (males in the mid- and top-dose groups and females in the top dose group). Statistically significant increases in relative spleen weights (males only in the top-dose group), liver and ovaries (both only in females in the top-dose group).	[redacted] 2013
Range finding oral, dietary, 28 day	[redacted]: CD SD rats	Napropamide 0, 181/197, 303/320, 502/530, 861/873 and 1577/1604.	None set as range-finding study.	Effects seen from about 300 mg/kg bw/day	Decreased bw gain, mild anaemia, liver enzyme effects and increased liver weights from 303/320 mg/kg bw/day.	[redacted] (1988)
Range finding oral, dietary, 6 weeks	[redacted]:CD-1 (ICR) BR mice	Napropamide 0, 386/513; 580/737, 737/1054, 1123/1467 and 2257/2937.	None set as range-finding study.	Effects seen from 737 mg/kg bw/day in males and 1467 mg/kg bw/day in females.	Increased liver weight at 737 mg/kg bw/day in males and from 1467 mg/kg bw/day in females.	[redacted] (1988)
Range-finding, oral, gavage, 4 weeks	Beagle dogs	Napropamide 30/1000, 60, 125, 250, 500 mg/kg bw/day	None set as range-finding study.	Effects at 1000 mg/kg bw/day	Decreased food consumption and body weights at 1000 mg/kg bw/day.	[redacted] (1987)
Oral, dietary 90-day	RccHan: WIST strain rats	**Napropamide-M** 0, 46/50, 185/203, 778/872 mg/kg bw/day Napropamide racemate (top dose only): 745/843 mg/kg bw/day	46 mg/kg bw/day for males and 50 mg/kg bw/day for females	Effects seen from 185/203 mg/kg bw/day in males and females, respectively.	Reduced erythrocyte count and other related secondary effects at 185/203 mg/kg bw/day, below range of historical control data.	[redacted] 2014
Oral, dietary 13 weeks	Sprague-Dawley rats	Napropamide 13, 25, 50 mg/kg bw/day	50 mg/kg bw/day	No effects seen at the highest dose tested, of 50 mg/kg bw/day.	No significant effects seen.	[redacted] (1970)
Oral, dietary, 13 weeks	Beagle dogs	Napropamide 16, 40, 100 mg/kg bw/day	40 mg/kg bw/day	100 mg/kg bw/day	Body weight loss, increased absolute and relative liver weights in males, increased alkaline phosphatase in females, decreased haemoglobin and haematocrit values in both sexes at 100 mg/kg bw/day.	[redacted] [redacted] (1970)
Oral, 52 weeks	Beagle dog	Napropamide 10, 70, or 500 mg/kg bw/day	500 mg/kg bw/day	>500 mg/kg bw/day	No adverse effects.	[redacted] [redacted] (1988)
Oral, 52 weeks	Beagle dog	Napropamide 50, 250, or 1000 mg/kg bw/day	50 mg/kg bw/day	250 mg/kg bw/day	Vomiting and liquid faeces at 250 and 1000 mg/kg bw/day, reduced body weight gains and increased absolute and relative liver weights at 1000 mg/kg bw/day. Albumin and alkaline phosphatase were decreased at 1000 mg/kg bw/day	[redacted] (1995)

Type of study	Species	Dose levels tested mg/kg bw/day	NOAEL	LOAEL	Findings	Reference
Dermal, 30 days	Wistar rat	Napropamide 10, 100, 1000 mg/kg bw/day	1000 mg/kg bw/day	>1000 mg/kg bw/day	No effects seen.	[redacted] (1991)

2.6.4. Summary of genotoxicity

Four *in vitro* and one *in vivo* studies conducted on napropamide-M were submitted for the purpose of this approval. Supplementary information was provided by *in vitro* and *in vivo* studies conducted on napropamide racemate and previously evaluated for the approval of that active substance.

The *in vitro* bacterial gene mutation study on napropamide-M confirmed a lack of any gene mutation potential in bacteria when using the plate incorporation methodology (when tested up to a suitable maximum concentration). A recent mammalian gene mutation study on napropamide-M revealed an equivocal result in mouse lymphoma cells in the presence of metabolic activation, whilst a clearly negative result was obtained without metabolic activation. A repeat of this test, conducted in accordance with the current (2016) OECD 490 guideline, confirmed that napropamide-M induced mutation at the tk locus in the presence of metabolic activation. Both large (indicating point mutations) and small (indicating chromosomal damage) colonies were increased, although the proportion of small colonies was increased compared with the solvent control cultures. Two mammalian gene mutation studies performed with napropamide (and evaluated for the approval of napropamide) both also gave positive results with metabolic activation (information on colony size not available). It is therefore concluded that napropamide-M is genotoxic in the *in vitro* mammalian cell gene mutation test.

Napropamide-M was negative in an *in vitro* chromosome aberration assay when tested up to an appropriate maximum concentration.

No increase in bone marrow micronucleus frequency was observed in two independent *in vivo* mouse bone marrow micronucleus studies conducted on napropamide technical (racemate), following oral administration of doses well in excess of the limit dose. ADME data (see Section B.6.1.1) confirms that, following oral administration, napropamide-M is rapidly absorbed from the GI tract; the concentration of the administered radioactivity was highest in blood and tissues 6 hours after dosing. Quantifiable radioactivity was measured in bone marrow in rats dosed with napropamide racemate. It is therefore reasonable to conclude that the bone marrow would have been extensively exposed to napropamide. The RMS considers these two studies to give valid negative results.

The biological relevance of the increases in mutant frequency observed in the *in vitro* mammalian gene mutation assay were investigated in an *in vivo* liver comet assay conducted with napropamide-M. Under the conditions of this comet assay, two oral administrations of napropamide-M up to the recommended maximum dose did not induce DNA damage in the liver of male rats.

In summary, napropamide-M was positive in an *in vitro* mammalian cell gene mutation test in the presence of S9. The proportion of small to large colonies was approximately 50 %, which was an increase in small colonies compared with the solvent control. Reassurance that napropamide-M was not clastogenic was provided by a negative *in vitro* chromosome aberration test conducted with this test material, and by two negative *in vivo* micronucleus tests conducted with the racemate. A new *in vivo* comet assay conducted with napropamide-M demonstrated that the active substance was not mutagenic *in vivo* when tested at doses up to the maximum recommended.

Both the mutagenic and clastogenic potential of napropamide-M (supplemented with information on the racemate) have been adequately investigated. The overall conclusion is that napropamide-M is not genotoxic *in vivo*.

According to the criteria of Regulation 1272/2008, no classification is warranted with respect to germ cell mutagenicity.

Table 2.6.4 Summary of *in vitro* and *in vivo* genotoxicity studies

Study type	Test system	Dose / concentration range (batch / purity)	Result
In vitro reverse mutation assay in bacteria (Ames test) OECD 471 (1997); GLP CA 5.4.1.1/01 Sokolowski (2010, 2011) No.: 1365602	*S. typhimurium* strains TA 1535, TA 1537, TA 98, TA 100; *E. coli* strain WP2 uvrA; plate incorporation and pre-incubation assay With/without S9-mix	Napropamide-M 0 - 5000 µg/plate in DMSO Tested in triplicate **Purity** Total D+L: 97.2 %, D-isomer: 96.71 %, L-isomer: 0.49 %	Negative
In vitro forward mutation assay in mammalian cells (mouse lymphoma assay) OECD 476 (1997); GLP CA 5.4.1.2/01 Wollny, 2011 No.: 1365603	Mouse lymphoma L5178Y cells With/without S9-mix Thymidine kinase ($tk^{+/-}$) locus	Napropamide-M 0 to 112 µg/ml[(a)] (4 h -S9) 0 to 56 µg/ml[(b)] and 0 to 28 µg/mL[(b)] (4 h +S9) 0 to 112 µg/ml[(b)] (24 h -S9) Dissolved in acetone Tested in duplicate in two independent experiments **Purity** Total D+L: 97.2 %, D-isomer: 96.71 %, L-isomer: 0.49 %	Equivocal +S9 Negative -S9
In vitro L5178Y Gene Mutation Assay at the tk locus OECD 490 (2016); GLP CA 5.4.1.2/02 Ballantyne, M., 2017 No.: 8357643	Mouse lymphoma L5178Y cells With/without S9-mix Thymidine kinase ($tk^{+/-}$) locus	Napropamide-M Short term treatment ***3 hours, -S9*** 50 to 250 µg/mL ***3 hours, +S9*** 0.5 to 10 µg/mL Continuous treatment **24 hours, -S9** 15 to 80 µg/mL Purity 97.98%	Positive +S9 Negative -S9
In vitro forward mutation assay in mammalian cells (mouse lymphoma assay) OECD 476 *Not submitted in napropamide-M dossier.* Majeska, 1984a	Mouse lymphoma L5178Y cells.	Napropamide racemate 0.012 – 0.024 mg/ml -S9 0.010 – 0.080 mg/ml +S9 Purity 94.6 % (total D- + L-isomer) (WRC 4921-27-24)	Positive (+/-S9)
In vitro forward mutation assay in mammalian cells OECD 476 *Not submitted in napropamide-M dossier.* Pirovano R. (1986a)	Chinese hamster V79 lung cells	Napropamide racemate 10, 50, 100 and 150 µg/ml -S9 mix, 5, 10, 50 and 100 µg/ml +S9 mix Purity 92 % (total D- + L-isomer) (BDH 1003)	Positive (+S9) Negative (-S9)

Study type	Test system	Dose / concentration range (batch / purity)	Result
In vitro Mammalian Chromosome Aberration Test OECD 473 (1997); GLP CA 5.4.1.3/01 Bohnenberger (2011) No.: 1365604	Human lymphocytes With/without S9-mix	Napropamide-M 109.7 to 1800 µg/ml[(c)] (4 h -S9) 0.7 to 2.2 µg/ml[(a)] (4 h +S9) 35.8 to 109.7 µg/ml[(d)] (22 h -S9) Dissolved in acetone **Purity** Total D+L: 97.2 %, D-isomer: 96.71 %, L-isomer: 0.49 %	Negative
In vivo Rat Alkaline Comet Assay OECD 489 (2016); GLP [redacted] (2017) No.: 8361879	Male Han Wistar rats	Napropamide-M Two doses of 0, 500, 1000 or 2000 mg/kg bw/d separated by 21 h (6 male rats/group) **Purity** 97.98% (total D- + L-isomer)	Negative
In vivo micronucleus test Comparable to OECD 474 (1984); Conducted prior to GLP CA 5.4.2/01 [redacted] (1984b) No.: T-11822	Male and female CD-1 mice, 5/sex/dose group/time point of sacrifice; two consecutive oral (gavage) doses, approximately 24 hours apart.	Napropamide racemate 0, 556, 1667, 5000, 5000 mg/kg bw in 10 % ethanol/corn oil 1000 polychromatic erythrocytes evaluated per animal Purity 94.6 % (total D- + L-isomer)	Negative
In vivo micronucleus test Comparable to OECD 474 (1984); Conducted prior to GLP [redacted]1986) No.: T-12813	Female CD-1 mice, 5/dose group; single oral (gavage) dose.	Napropamide racemate 0, 556, 1667, 5000, 5000 mg/kg bw in 10 % ethanol/corn oil 1000 polychromatic erythrocytes evaluated per animal Purity 94.6 % (total D- + L-isomer)	Negative

(a): Maximum dose was limited by solubility in the test system; precipitation observed by eye at the end of treatment
(b): Maximum dose was limited by toxicity in the test system, with RTG reduced to between 10-20 %
(c): Precipitation observed by eye at the end of treatment at all doses.
(d): Maximum dose was limited by toxicity in the test system, with an MI of 52 %

2.6.5. Summary of long-term toxicity and carcinogenicity

Long-term and carcinogenicity studies are available on napropamide racemate administered by the oral route in rats and mice, all of which were previously evaluated by Denmark for the approval of that substance. No studies on napropamide-M were submitted. However, the RMS considers that the studies on the racemate are sufficient to inform on the carcinogenic potential of the isomer.

The chronic toxicity and carcinogenicity of napropamide racemate have been investigated in two acceptable rat studies. In a 24-month toxicity/oncogenicity study, a number of adverse effects were seen in animals dosed at the high-dose levels of 5000 and 10,000 ppm (satellite group, terminated at 12 months in accordance with the study protocol). These effects included decreased haematological parameters indicative of mild anaemia, small increases in gamma-glutamyl transferase activity and increased absolute and relative liver and kidney weights. In addition, decreased body-weight and body-weight gains and decreased food consumption occurred from

1100 ppm (47.56/55.31 mg/kg bw/day). At 24 months, cysts in the kidney and foci of discoloration in the liver in males and emaciation in females were seen at 5000 ppm, whilst histopathology revealed an increased severity of chronic progressive glomerulonephritis and an increased incidence of spongiosis hepatis of the liver in males at this dose. A NOAEL for chronic toxicity of 250 ppm (10.48/12.28 mg/kg bw/day in males and females, respectively) was set based on the effects on body-weights and food consumption from 1100 ppm. There was no increase in neoplasm incidence associated with napropamide exposure (NOAEL for carcinogenicity ≥ 5000 ppm). In the second rat study, a statistically significant decrease was observed in food consumption and body-weights at the high dose level of 100 mg/kg bw /day. Based on these findings, the NOAEL for chronic toxicity in this two-year study was 30 mg/kg bw/day. Napropamide was not carcinogenic in this study at doses up to 100 mg/kg bw/day.

In an 18-month mouse carcinogenicity study, treatment-related, statistically significant findings included decreased body weights and body weight gains and increased liver and kidney weights from 3500 ppm (455/568 mg/kg bw/day in males and females, respectively). Based on these results, a chronic NOAEL of 450 ppm (55 mg/kg bw/day for male and 70 mg/kg bw/day for females) was identified. Napropamide racemate was not carcinogenic in this study when tested up to 7000 ppm (equivalent to 931/1216 mg/kg bw/day for males/females, respectively). A second mouse study was available but judged not to be acceptable because of reporting deficiencies and inconsistencies

Overall, the RMS concludes that napropamide was not carcinogenic in acceptable studies in rats and mice. This is in agreement with the EFSA Conclusion of the peer-review of napropamide that *"no carcinogenic potential was observed in either rats or mice upon long-term exposure to napropamide"* and in the Appendix A (List of End Points) that *"napropamide is unlikely to pose a carcinogenic risk to humans".* The RMS proposes that no classification of napropamide-M for carcinogenicity is required.

Table 2.6.5 Summary of long-term toxicity and carcinogenicity studies

Type of study/ Species/ Purity	**Dose levels (napropamide racemate)**	**NOAEL Males/females mg/kg bw/day**	**LOAEL Males/females mg/kg bw/day**	**Findings**	**Reference**
Oral, 24 months Sprague Dawley Rat 94.1 % (total D- + L-isomer)	0, 250, 1100, 5000, 10,000 ppm corresponding to 0, 10.48/12.28, 47.56/55.31, 221.44/260.81, 521.57/583.82 mg/kg bw/day for males/females	Systemic toxicity 250 ppm (10.48/12.28 mg/kg bw/day) Carcinogenicity 10,000 ppm	Systemic toxicity 1100 ppm (47.56/55.31 mg/kg bw/day) Carcinogenicity >10,000 ppm	Decreased body weights and feed consumption from 1100 ppm. Haematological, clinical parameter changes from 5000 ppm Not oncogenic	[redacted] (1991a) Hodge (1993)
Oral, 24 months Sprague Dawley Rat 94.6 % (total D- + L-isomer)	0, 10, 30, 100 mg/kg bw/day	Systemic toxicity 30 mg/kg bw/day Carcinogenicity 100 mg/kg bw/day	Systemic toxicity 100 mg/kg bw/day. Carcinogenicity >100 mg/kg bw/day	Decreased feed consumption and body weights; increased liver weights. Not oncogenic	[redacted] (1978)
Oral, lifetime, mouse CD-1 mice 94 % and 94.6 % **Study unacceptable**	0, 10, 30, 100 mg/kg bw/day	30 mg/kg bw/day	100 mg/kg bw/day	Body weight loss and decreases in liver and kidney weights. Not oncogenic	[redacted] (1978a)

Type of study/ Species/ Purity	Dose levels (napropamide racemate)	NOAEL Males/females mg/kg bw/day	LOAEL Males/females mg/kg bw/day	Findings	Reference
Oral, 18-months, mouse CD-1 mice 94 3 % (total D- + L-isomer)	0, 60, 450, 3500, 7000 ppm corresponding to 0, 7.4/9.4, 55/70, 455/568, 931/1216 mg/kg bw/day for male/females	Systemic toxicity 450 ppm (55/70 mg/kg bw/day) Carcinogenicity 7000 ppm	Systemic toxicity 3500 ppm: 455/568 mg/kg bw/day in males and females Carcinogenicity >7000 ppm	Reduced body weights and body weight gains. Increased relative liver weights. Not oncogenic	[redacted] (1991b)

2.6.6. Summary of reproductive toxicity

No studies on the reproductive toxicity of napropamide-M were submitted. However, a three-generation reproduction study and several developmental toxicity studies conducted with the racemate were available, all of which were previously evaluated by Denmark for the approval of napropamide. Therefore, by applying a bridging approach, the data requirements for napropamide-M were met.

A three-generation rat reproduction study with two litters per generation did not reveal evidence of reproduction toxicity in doses up to 100 mg/kg bw/day given for approximately 100 days. In the high-dose group, parental toxicity consisted of decreased body weight in the F1 females at the beginning and termination of the generation, and in F2 males and females at the beginning of the generation. No treatment-related reproductive effects were observed; however, offspring toxicity (decreased body weight) occurred at the same dose level (100 mg/kg bw/day) that caused decreased body weight in the parental generation (secondary to the reduced maternal body-weight).

Two developmental toxicity studies with napropamide racemate were performed in rabbits. In one of these, some animals of the high-dose group (1000 mg/kg bw/day) showed reduced food consumption and reduced body-weight gain; despite this, there was no evidence of developmental toxicity in this study. The second rabbit study was not acceptable because of problems with the gavage administration of doses that resulted in severe maternal stress and thus confounding of the findings.

Three acceptable developmental toxicity studies on the racemate have been conducted in rats. A fourth rat study was not acceptable because of very low doses administered and uncertainty about the actual doses achieved.
In the acceptable studies, evidence of maternal toxicity comprised clinical signs of toxicity, decreased body weight gain and decreased food consumption in rats given the highest doses (400 mg/kg bw/day in one study, 1000 mg/kg bw/day in the other two studies). However, neither foetal nor developmental toxicity was apparent at any dose in any of these studies.

In conclusion, oral administration of napropamide racemate over three generations did not result in specific reproductive toxicity in male or female rats at doses up to 100 mg/kg bw/day. The NOAEL for fertility was therefore ≥ 100 mg/kg bw/d, whilst that for parental toxicity and offspring toxicity was 30 mg/kg bw/d. No adverse developmental effects of napropamide racemate were observed in the rat or rabbit after *in utero* exposure to doses that resulted in maternal toxicity (up to the limit dose of 1000 mg/kg bw/day). The NOAEL for maternal toxicity was 110 mg/kg bw/day in rats and 300 mg/kg bw/day in rabbits, whilst the NOAEL for developmental toxicity was ≥ 1000 mg/kg bw/d in rats and rabbits.

Although there are no studies on napropamide-M, given the similarity between the racemate and napropamide-M, already established on the basis of the acute toxicity, short term and genotoxicity studies, the RMS considers it to be appropriate to bridge from the database on napropamide racemate to conclude on the reproductive toxicity of napropamide-M.

The RMS proposes that no classification is required for reproductive toxicity for napropamide-M.

Table 2.6.6 Summary of reproductive toxicity studies

Type of study (purity)	Species	Dose range tested (napropamide racemate)	NOAEL	LOAEL and effects	Reference
Three-generation reproduction (94.6 %, total D- + L-isomer)	Sprague Dawley Rat	0, 10, 30, or 100 mg/kg bw/day	Parental: 30 mg/kg bw/day Pups: 30 mg/kg bw/day Fertility effects: 100 mg/kg bw/day	Parental: 100 mg/kg bw/day, based on reduced body weights Pups: 100 mg/kg bw/day, based on reduced body weights Fertility: >100 mg/kg bw/day, no effects at high dose	[redacted] (1978b), [redacted] (2007) and [redacted], 1981
Teratology-range-finding (21 day repeated dose study) Purity not stated	NZW Rabbit	0, 100, 300, 500 mg/kg bw/day	Range-finding study purity and batch number not given	300 mg/kg bw/day. Increased mortality and clinical signs	[redacted] (1984)
Teratology (94.6 %) **Study unacceptable**	NZW Rabbit	0, 10, 50, 200 mg/kg bw/day	The study was evaluated not to be acceptable because of high mortality due to dosing difficulties	Maternal toxicity: Abortions and liver changes from 50 mg/kg bw/day, decreased spleen weight at 200 mg/kg bw/day. Developmental tox: None	[redacted] (1984, 1985)
Teratology (94.6 %, total D- + L-isomer)	NZW Rabbit	0, 100, 300, 1000 mg/kg bw/day	Maternal: 300 mg/kg bw/day Developmental: 1000 mg/kg bw/day	Maternal tox: 1000 mg/kg bw/day. Decreased body weights and food consumption Fetotox/developmental tox: >1000 mg/kg bw/day – no effects seen	[redacted] (1990)
Teratology-range-finding (94.3 %, total D- + L-isomer)	Sprague Dawley Rat	0, 500, 750, 1000 mg/kg bw/day	Not relevant as range-finding study	1000 mg/kg bw/day: Reduced food consumption No effects on fetus/development	[redacted] (1989)
Teratology (94.3 %, total D- + L-isomer) **Study unacceptable**	Sprague Dawley Rat	0, 25 or 75 (purified racemate), 77 (napropamide racemate) mg/kg bw/day	The study is not acceptable because of study conduct and reporting shortcomings.	Maternal tox >77 mg/kg bw/day – no effects seen. Pups: Incomplete ossification of centra at all dose-levels	[redacted] [redacted] (1971)
Teratology (94.6 %, total D- + L-isomer)	Sprague Dawley Rat	0, 30, 110, 400 mg/kg bw/day	Maternal: 110 mg/kg bw/day Developmental: 400 mg/kg bw/day	Maternal: 400 mg/kg bw/day: decreased food consumption and clinical signs (stained or matted fur)	[redacted] (1982)
Teratology (94.3 %, total D- + L-isomer)	Sprague Dawley Rat	0, 100, 300, 1000 mg/kg bw/day	Maternal: 300 mg/kg bw/day Developmental: 1000 mg/kg bw/day	Maternal: 1000 mg/kg bw/day: reduced food consumption and body weight gain – decreased reproductive performance (high non-pregnant rate), which also occurred in controls. Fetal and developmental >1000 mg/kg bw/day as no effects were seen	[redacted] (1990a)

Type of study (purity)	Species	Dose range tested (napropamide racemate)	NOAEL	LOAEL and effects	Reference
Teratology (94.3 %, total D- + L-isomer)	Sprague Dawley Rat	0 and 1000 mg/kg bw/day	Maternal: <1000 mg/kg bw/day Developmental: 1000 mg/kg bw/day	Maternal: 1000 mg/kg bw/day: reduced food consumption and body weight gain. Fetal/Developmental: >1000 mg/kg bw/day, as no effects were seen.	[redacted] (1990b)

2.6.7. Summary of neurotoxicity

Napropamide-M does not have a structure similar or related to those capable of inducing neurotoxicity, and the 90-day toxicity study on napropamide-M in the rat did not show specific indications of potential neurotoxicity. Furthermore, the toxicology studies submitted on napropamide racemate revealed no evidence of specific neurotoxicity. Therefore, neurotoxicity studies on rodents are not required for napropamide-M.

2.6.8. Summary of further toxicicological studies on the active substance

No supplementary studies on the active substance were submitted. The RMS agrees that none were required. In particular, napropamide-M does not meet the interim criteria for the identification of a substance with endocrine-disrupting properties under Regulation EC 1107/2009, nor did it demonstrate any evidence of endocrine effects in any of the studies; therefore, studies to investigate endocrine activity were not required.

2.6.9. Summary of toxicological data on impurities and metabolites

For napropamide-M there were no relevant metabolites in groundwater, surface water, soil or air observed in environmental fate and behaviour studies that needed to be considered from a toxicological point of view.

2.6.10. Summary of medical data and information

The applicant reported that occupational health surveillance medical examinations at the Sandbach and Gujarat production sites had not identified any health problems resulting from working with napropamide-M.

Based on information from the manufacturing plant, as well as a review of published literature, it is concluded that there have been no reported incidents of napropamide-M poisoning in humans.

No direct observations of clinical cases or poisoning incidents with napropamide were submitted.

No information on epidemiological studies was submitted.

The applicant's literature search did not return any relevant results.

2.6.11. Toxicological end point for assessment of risk following long-term dietary exposure – ADI

Toxicological studies were available on napropamdide-M and napropamide racemate. The RMS concludes that napropamide-M (i.e. the R isomer) and the racemate have equivalent toxicity and it is thus appropriate, where information is not available on napropamide-M itself, to bridge from the existing toxicology studies on napropamide racemate to napropamide-M to meet the data requirements.

Six repeated dose and chronic studies and one three-generation study are available as a basis for setting an ADI. The effects seen in repeated dose toxicity studies were primarily effects on food consumption, body weights and the blood system (mild anaemia). Occasionally, liver weights were increased.

Table 2.6.7 Summary of studies relevant for setting an ADI

Study type	Dose levels (napropamide racemate)	NOAEL	LOAEL	Effects	Reference
Oral, 52 weeks Beagle dog	10, 70, or 500 mg/kg bw/day	500 mg/kg bw/day	>500 mg/kg bw/day	No adverse effects.	[redacted] (1988)
Oral, 52 weeks Beagle dog	50, 250, or 1000 mg/kg bw/day	50 mg/kg bw/day	250 mg/kg bw/day	Vomiting and liquid faeces at, reduced body weight gains	[redacted] (1995)

Study type	Dose levels (napropamide racemate)	NOAEL	LOAEL	Effects	Reference
Oral, 24 months chronic/carcinogenicity, rat	0, 250, 1100, 5000, 10000 ppm (0, 10.48 / 12.28, 47.56 / 55.31, 221.44 / 260.81, 521.57 / 583.82 mg/kg bw/day for males / females)	250 ppm (10.48 / 12.28 mg/kg bw/day)	1100 ppm (47.56 / 55.31 mg/kg bw/day)	Decreased body weights and feed consumption.	[redacted] (1991a) [redacted] (1993)
Oral, 24 months chronic/carcinogenicity, rat	0, 10, 30, 100 mg/kg bw/day	**30 mg/kg bw/day**	100 mg/kg bw/day.	Decreased feed consumption and body weights; increased liver weights.	[redacted] (1978) [redacted] (1986)
Oral, 18-months, chronic/carcinogenicity, mouse	0, 60, 450, 3500, 7000 ppm (0, 7.4/9.4, 55/70, 455/568, 931/1216 mg/kg bw/day for male/females)	450 ppm (55 / 70 mg/kg bw/day)	3500 ppm: 455 / 568 mg/kg bw/day in males / females	Reduced body weights and body weight gains. Increased relative liver weights and relative kidney weights.	[redacted] (1991b)
3-generation reproduction, rat	0, 10, 30, or 100 mg/kg bw/day	30 mg/kg bw/day	100 mg/kg bw	Decreased body weights	[redacted] (1978b)

The available long-term studies in rats, mice and dogs all indicated a NOAEL of 10-70 mg/kg bw/day. The highest NOAEL below the lowest LOAEL was 30 mg/kg bw/d from one of the rat carcinogenicity studies. This value was supported by the same NOAEL in the rat three-generation study, with a LOAEL value of 100 mg/kg bw/d. The NOAELs (55 - 500 mg/kg bw/d) and LOAELs (250 - >500 mg/kg bw/d) from the dog studies were higher than those from the rat studies, indicating that the rat was the most sensitive of these species. The NOAEL of 30 mg/kg bw/d from the rat carcinogenicity study is therefore the most appropriate value to use in the derivation of an ADI.
In the calculation of the ADI, application of the standard factors of 10 to account for inter-species extrapolation and 10 to account for intra-species variability is proposed.

The proposed ADI is:

ADI = 30 mg/kg bw/day/100 = **0.3 mg/kg bw/day**.

This proposal is in accordance with the applicant's own proposal.

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

No specific effects are associated with acute exposure to napropamide-M and it is of low acute oral toxicity (LD_{50} > 2000 mg/kg bw). Body weight effects are seen at the start of dosing in developmental studies when high doses are administered (e.g. 1000 mg/kg) and these effects might trigger an ARfD. However, the effects were previously considered; the EFSA Conclusion (EFSA, 2010) of the peer-review of napropamide states:

"Considering the critical effects observed in the short-term studies, the experts did not consider that they were relevant for an acute exposure. Taking into account the entire toxicological profile of the substance, the experts agreed not to set an ARfD".

There are no new data and therefore the RMS agrees with the conclusion reached previously; an ARfD is not proposed for napropamide-M.

2.6.13. Toxicological end point for assessment of occupational, bystander and residents risks – AOEL

Napropamide is of low acute oral, dermal and inhalational toxicity. Napropamide is not considered to possess a carcinogenic or genotoxic potential. It is not toxic to reproduction or development. Based on this, the oral short-term studies are considered relevant for the allocation of the AOEL.

A number of sub-chronic studies in rats and dogs and a three-generation study in rats were considered as the basis for setting the acceptable operator exposure level. The NOAELs identified in these studies generally ranged from 30-70 mg/kg bw. The adverse effects were consistent across the studies, comprising haematological effects that indicated mild anaemia, body-weight changes and liver effects.

The highest NOAEL below the lowest LOAEL was 50 mg/kg bw/d, in the 90-day napropamide-M study, the 90-day napropamide racemate study, and a 52-week dog study. Since dogs appeared to have a lower sensitivity to napropamide-M / napropamide racemate toxicity, as noted above, and because the sub-chronic study duration is the most appropriate for the AOEL, the value of 50 mg/kg bw/d from the two rat 90-day studies (one with napropamide-M, one with the racemate) will be used as the basis for the AOEL.

Table 2.6.8 Summary of studies relevant for setting an AOEL

Type of study; species	Dose levels tested mg/kg bw/day	NOAEL	LOAEL	Findings at the LOAEL	Reference
Oral, dietary 90-day	**Napropamide-M** 0, 46/50, 185/203, 778/872 mg/kg bw/day Napropamide racemate (top dose only): 745/843 mg/kg bw/day	46 / 50 mg/kg bw/day in males and females, respectively	185/203 mg/kg bw/day in males and females, respectively.	Reduced erythrocyte count and other related secondary effects at 185/203 mg/kg bw/day	[redacted] 2014
Oral, dietary 90 days Sprague-Dawley rats	Napropamide 13, 25, 50 mg/kg bw/day	50 mg/kg bw/day	-	No significant effects seen.	[redacted] (1970)
Oral, dietary, 90 days Beagle dogs	Napropamide 16, 40, 100 mg/kg bw/day	40 mg/kg bw/day	100 mg/kg bw/day	Weight loss, increased absolute and relative liver weights in males, increased alkaline phosphatase in females, decreased haemoglobin and haematocrit in both sexes at 100 mg/kg bw/day.	[redacted] (1970)
Oral, 52 weeks Beagle Dog	Napropamide 10, 70, or 500 mg/kg bw/day	500 mg/kg bw/day	>500 mg/kg bw/day	No adverse effects.	[redacted] (1988)
Oral, 52 weeks Beagle Dog	Napropamide 50, 250, or 1000 mg/kg bw/day	50 mg/kg bw/day	250 mg/kg bw/day	Vomiting and liquid faeces.	[redacted] (1995)
Three-generation reproduction, rat	Napropamide 0, 10, 30, or 100 mg/kg bw/day	30 mg/kg bw/day	100 mg/kg bw	Decreased body weights.	[redacted] (1978b)

Since absorption of napropamide is >90% following oral administration, adjustment for oral absorption is not required. The standard factors of 10 for each of inter-species and intra-species differences are proposed.

AOEL= 50 mg/kg bw/day (100% oral absorption)/100 = 0.50 mg/kg bw/day.

This proposal is in accordance with the proposal from the applicant.

2.6.14. Toxicological end point for assessment of occupational, bystander and residents risks following acute exposure – AAOEL

As noted under section 2.6.12, no specific effects were associated with acute exposure to napropamide-M, and it is of low acute toxicity. The RMS thus did not consider it necessary to set an ARfD, nor is an AAOEL required.

2.6.15. Summary of product exposure and risk assessment

Operator exposure estimates using the German Model and UK POEM indicate that the proposed application of **'**D-Devrinol 450-SC' will result in an acceptable risk to operators (as detailed in Table 2.6.14-1).

Table 2.6.14-1 Operator exposure to napropamide-M resulting from the proposed use of 'D-Devrinol 450-SC': summary of estimates indicating an acceptable risk

Proposed use	Application method	Model/data	Operator protection	% of AOEL
Brassica vegetables & winter oil seed rape	Tractor-mounted field crop boom sprayer	German model	NO PPE	17%
		UK POEM	No PPE	100%

On the basis these estimates and considering the product is not classified for human health, the proposed use of 'D-Devrinol 450-SC' is considered to be acceptable with no operator protection requirements.

Bystander and resident exposure assessments also indicate an acceptable level of risk, as surmised in table 2.6.14-2.

Table 2.6.14-2 Bystander and resident exposure to napropamide-M resulting from the proposed use of 'D-Devrinol 450-SC': summary of estimates indicating an acceptable risk for unprotected bystanders and residents

Proposed use	Application method	Model/data	% of AOEL
Brassicas & oil seed rape	Tractor-mounted field crop boom sprayer	UK approach – vapour exposure Californian EPA surrogate study	<1% adults 2% children
Brassicas & oil seed rape	Tractor-mounted field crop boom sprayer	UK approach – drift exposure Simulated bystander exposure measurements (Lloyd and Bell)	<1% adults
Brassicas & oil seed rape	Tractor-mounted field crop boom sprayer	UK approach – exposure to drift fallout US EPA values for residential exposure	<1% children
Brassicas & oil seed rape	Tractor-mounted field crop boom sprayer	German (BfR) approach – exposure to bystanders	<1% adults <1% children
Brassicas & oil seed rape	Tractor-mounted field crop boom sprayer	German (BfR) approach – exposure to residents	<1% adults <1% children

'D-Devrinol 450-SC' is applied directly to the soil pre-emergence of the oil seed rape and brassica vegetable crops. The potential for subsequent worker exposure following this method of application is therefore considered negligible, and a worker re-entry risk assessment is not considered necessary.

2.7. RESIDUE

2.7.1. Summary of storage stability of residues

Storage stability studies have been provided which demonstrate that residues of napropamide are stable when stored at -18ºC or below for up to 341 days in high water content commodities (cabbage) and 12 month in high

oil content commodities (oil seed rape seed). Recovery after storage was > 75% in both studies: therefore, the data on napropamide were considered acceptable to address the storage stability of napropamide-M.

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

Six metabolism studies conducted on plants have been provided. The details of the studies have been summarised in Table 1.1.2-1 below.

Table B.1.1.2-1: Summary of the primary plant metabolism studies

Crop groups	Crop	Label position	Application and sampling details				Study
			Method	Rate	No	Sampling (DAT)	
Fruit crops	Tomato	^{14}C-1-naphthyl]-napropamide	Soil incorporated to top 5cm. Glasshouse study. Tomato seedlings transplanted into treated soil at 4-6 leaf stage.	Corresponding to 2.5 kg as/ha	1	Tomatoes harvested as they ripen.	Webb, J., Allin, R., Joseph, R.S.I. (1992)
	Apple	^{14}C-1-naphthyl]-napropamide	Soil incorporated to top 5-8 cm around 3 year old trees. Then second application 155 days later watered on.	1) Corresponding to 4.61 kg as/ha. 2) Corresponding to 4.53 kg as/ha. Total= 9.15 kga s/ha	2	At harvest 35 days after last treatment and 550 DAT.	Hurt, AD, Joseph, R.S.I, 1992
Root crops	Potato	[^{14}C-1-naphthyl]-napropamide	Soil incorporated to top 2.5cm. Outdoor pot study.	Corresponding to 2 kg as/ha.	1	At harvest 61 days after last treatment.	Spillner,C.J., 1983
Leafy crops	Cabbage	[^{14}C-1-naphthyl]-napropamide	Soil incorporated to top 5cm. Glasshouse study. Cabbage seedlings transplanted into treated soil at 6-8 leaf stage.	Corresponding to 2.5 kg as/ha	1	55-60 DAT. Cabbage heart and whole cabbage.	Emburey & Joseph (1992)
Pulses/Oilseeds	Oilseed rape	[^{14}C-1-naphthyl]-napropamide	Soil incorporated to top 3-4 cm. Outdoor Rape seeds sown into treated soil	Corresponding to 2.0 kg as/ha	1	Forage 124 and 195 DAT and immature pods 256 DAT and harvestable pods 292 DAT	Langford-Pollard A.D., 2002
	Oilseed rape	[^{14}C-1-naphthyl]-napropamide-M	Soil incorporated to top 2.5 cm. Rape seeds sown into treated soil. Kept in glasshouse until BBCH 12, then outdoors.	Corresponding to 0.72 kg as/ha	1	Forage at BBCH 15, 22 and 51, pods and foliage at GS 76 and pods, straw and seed at BBCH 84.	Ahmad, S. (2015)

All of the studies except for the Ahmad, 2015 study have been conducted using napropamide and previously evaluated in the napropamide DAR which concluded as follows:

The metabolism of napropamide has been investigated in cabbage (leafy crops), tomatoes (fruiting vegetables), oilseed rape (oilseed), potatoes (root and tuber) and apples (fruit). In all cases except the apple study, plants were sown in soil treated with [^{14}C]-napropamide. The metabolism of napropamide in the four crop categories is similar.

In cabbage, tomatoes, oilseed rape and potato peel napropamide was detected in trace amounts (<0.01 mg/kg). No napropamide was detected in potato pulp.

In cabbage and tomatoes seven and nine metabolites were detected, respectively. In potato pulp and peel traces of several metabolites, all < 0.01 mg/kg were detected. In oilseed rape up to eighteen components were detected. In forage from oilseed a significant amount of unmetabolised napropamide was detected (0.054

mg/kg). Here all other components were present at < 0.05 mg/kg, although some accounted for > 10% of TRR in forage samples and foliage from immature plants. In all other cases metabolites were found in amounts < 0.01 mg/kg and < 10% of TRR.

In the metabolism study in apples in which soil around apple trees was treated with [^{14}C]-napropamide, TRR in the mature fruit was negligible (< 0.01 mg/kg).

The metabolism of napropamide involved the following routes:

1) *Desethylation to desethylnapropamide (DE-NPAM) followed by further desethylation to naphthoxypropionamide (NOPAM) and then hydrolyses to naphthoxypropionic acid (NOPA).*
2) *Hydroxylation of position 5 in the ring to give 5-hydroxynapropamide (5-OH-NPAM), which is the major metabolite in whole cabbage, followed by desethylation of this compound to give 5-hydroxydesethylnapropamide (5-OH-DE-NPAM). This was hydrolysed to give 5-hydroxynaphthoxypropionic acid (5-OH-NOPA).*
3) *Hydroxylation of position 4 in the ring to give 4-hydroxy-napropamide (4-OH-NPAM), desethylation of this compound to give 4-hydroxynaphthoxypropionic acid (4-OH-NOPA). Oxidation of this compound resultet in 1.4-naphthoxyquinone (NQ) and further oxidation of (NQ) gives compound o-phthalic acid (PA). NQ and PA were only found in conjugated forms*.

The rapporteur has evaluated that the metabolic pattern found in leafy crops, fruiting vegetables, root and tuber vegetables are similar. In oilseed rape napropamide is metabolised extensively since up to eighteen compounds are seen. RMS supposes that the metabolic pattern of napropamide in oilseed is similar to the metabolism found in the three crop categories. No further studies are required for elucidating the metabolic pathway of napropamide in plants.

The metabolic pathway for napropamide in plants is the same as in the rat.

A residue definition of napropamide in plants for both monitoring and risk assessment was therefore proposed. During peer review, concerns were raised that restricting the residue definition to napropamide only could substantially underestimate the total toxicological burden. This was summarised in the EFSA conclusion (EFSA Journal 2010; 8(4):1565):

The RMS proposed to restrict the residue definition to napropamide for monitoring and risk assessment. This was agreed by the PRAPeR 35 meeting of experts. It was however noted that the definition for risk assessment may underestimate by 1 to 2 orders of magnitude the global toxicological burden, considering the ratio between the parent compound and all metabolites produced by plant metabolism. This was however considered of no consequence in the final outcome of the risk assessment, given the very low portion of the ADI used. The possible change in the ratio of constituting isomers by plant metabolism or due to environmental conditions was also considered by the meeting of experts. It was considered that the impact on consumer safety would not be an issue in this case, as the exposure is minimal.

For this evaluation of napropamide-M, one additional metabolism study has been provided (Ahmad, 2015) where dosing with napropamide-M was performed on soil in which oilseed rape was then cultivated. Although significant attempts to extract residues were performed in the study very little characterisation was possible. The study was performed at approximately 1N and significant extractable residues (above 0.01 mg/kg in food and >0.05 mg/kg in feed) were only found in foliage at pod development and haulm at maturity. Considering the low levels of residues found in rapeseed and the margin of safety shown in the consumer risk assessment, additional studies to elucidate further potential differences in napropamide and napropamide-M metabolism were not considered warranted.

No detectable residues of napropamide-M were present in plant commodities therefore expected residues intakes by livestock are <0.004 mg/kg bw/day and metabolism studies in animals (and a residue definition for animal commodities) were not necessary. Napropamide metabolism studies have however been conducted in lactating goats and laying hens. In both goats and hens napropamide is rapidly excreted and extensively metabolised. No feeding studies were conducted or required given that the animal exposure is minimal.

2.7.3. Definition of the residue

Plant residue definition for monitoring: Napropamide (sum of the *R*- and *S*- isomers at any ratio)

Plant residue definition for risk assessment: Napropamide (sum of the *R*- and *S*- isomers at any ratio)

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

Brassica vegetables

Twenty six residue trials on brassica vegetables have been submitted. All trials were performed using a single application of napropamide formulated as 450 g/l suspension concentrate. The formulation was applied to the soil using a commercial sprayer at about 1.0 kg as/ha napropamide prior to transplanting of the seedlings. In all cases residues of napropamide were below the LOQ. The LOQ was 0.1 mg/kg in the four trials from year 2000 and 0.01 mg/kg in all other trials. Procedural recoveries for all trials were within 77- 106%, one unacceptable procedural recovery occurred in Clark, 2002c, AS/5634/US but samples from this batch were reextracted.

It should be noted that all the brassica trials involved application of napropamide which is a racemate of the R and S isomer. Therefore all the application rates have been halved to be appropriate to napropamide-M. On this basis the application rate for the trials is between 0.48 to 0.53 kg as/ha which is not within ±25% of the GAP (0.765 kg as/ha). However, the residues in all trials have been shown to be <LOQ. In addition, the residues have been determined as napropamide the racemate form. Therefore the residues of napropamide-M could also be half of that shown in the trials. Even if residues at twice the current LOQ were to be found in trials at the proposed GAP there is a considerable margin of safety for the risk assessment based on the proposed ADI (0.3 mg/kg bw/day).

Crop	Trials relevant to the representative uses		MRL[+]	HR[+]	STMR[+]
Cauliflower	NEU	4 x <0.1, <0.01, 3 x <0.01	0.02*	0.02	0.02
	SEU	2 x <0.01			
Cabbage	NEU	3 x <0.1, 4 x <0.01			
	SEU	2 x <0.01			
Brussels sprout	NEU	4 x <0.1 4 x <0.01			
	SEU	-			

[+]Note as the residues are determined as napropamide in the available residue trials, residues have been doubled to enable a conservative risk assessment to be conducted.

The residues in all trials were demonstrated to be below the LOQ (0.01 and 0.1 mg napropamide/kg). The following extrapolation is possible for applications before the edible part of the crop is formed (i.e. BBCH 16). Based on the residues being <LOQ in all the trials, eight trials on cabbage and eight trials on cauliflower are not considered to be required and a reduced data set is acceptable.

8 trials on head cabbages (0242020) → Whole subgroups
+ (a) flowering brassica (0241000) and
8 trials on cauliflower (0241020) (b) head brassica (0242000)

Note extrapolation cannot be made to leafy brassicas (0243000) or kohl rabi see SANCO 7525/VI/95 Rev. 10.2

Oilseed rape
Eighteen trials on oilseed rape have been submitted. Of these, four residue trials conducted in northern France using a single application of napropamide (450 g/l SC) and seven residue trials using a single application of napropamide-M, formulated as D-Devrinol 45 SC, were considered appropriate to the GAP. The LOQ was 0.05 mg/kg in the four trials conducted with napropamide and 0.01 in the seven trials conducted with napropamide-M. Procedural recoveries for rape seed in all trials were within 71- 106%, for whole plants recoveries were within 66-101% and for immature pods 61-91 %.

It should be noted that four trials have been provided involving application of napropamide which is a racemate of the R and S isomer. Therefore the application rates in these trials have been halved to be appropriate to napropamide-M.

Residues at harvest in all cases were below or equal to the LOQ. There were sufficient residue trial data to support the proposed use based on the Napropamide-M residue trials; the napropamide trials pertinent to the GAP are also shown in the below table as supporting information.

Crop		Napropamide-M	Napropamide	MRL required	HR	STMR
Oilseed rape	NEU	3 x <0.01	4 x <0.05	0.01	0.01	0.01
	SEU	4 x <0.01				

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

Expected residues intakes by livestock are <0.004 mg/kg bw/day and therefore feeding studies have not been submitted and were not required.

2.7.6. Summary of effects of processing

Processing studies have not been submitted and were not required.

2.7.7. Summary of residues in rotational crops

A napropamide rotational crop metabolism study and rotational crop trials for wheat (grown after oilseed rape) have been provided. Both of the studies have been previously evaluated in the napropamide DAR which concluded as follows:

The cultivation of certain crops within one year after the use of napropamide may cause problems due to phytotoxic effects. A confined rotational crop study was carried out using carrots, lettuce, and wheat as succeeding crops, planted 60, 180 and 360 days after soil treatment at 4800 g a.s./ha. This application rate is 5N in case of brassicas, 4N in case of oilseed rape, and 2N in case of tomatoes. Under these circumstances the TRR were ranging from 0.08 (lettuce) to 0.41 mg/kg (wheat forage) for the 60 days interval, and decreased to 0.04 (lettuce and carrot roots) to 0.11 mg/kg (wheat grain) for the 360 days interval. Unchanged napropamide was found in mature commodities at levels generally below 0.01 mg/kg, except in carrot roots, where the levels were 0.05 and 0.02 mg/kg for the 60 days and 180 days intervals, respectively. Two metabolites were identified, suggesting that the metabolism in rotational crops is similar to that in primary crops. In a field study, where wheat was cultivated as a rotational crop to oilseed rape, residues in straw and grains were below the LOQ of 0.01 mg/kg.

The information available suggests a potential for low but measurable napropamide residues in rotational crops, particularly in root crops. The RMS proposed a waiting period of 180 days from the use of napropamide before planting or sowing rotational crops. This should be considered at Member State level.

The conclusions from the napropamide EU peer review can be considered appropriate for napropamide-M. Residues are low in succeeding crops and the data suggests residues will be <0.01 mg/kg after 180 days.

The PEC_{soil} accumulation for napropamide-M is 1.5979 mg/kg (see Vol 1, 2.8.6); this equates to an application rate of approximately 1198 g as/ha. At this rate significant residues in following crops are not expected as long as the interval between last application and planting of succeeding crops is in excess of180 days.

It is noted that the rotational crop metabolism study indicates that residues of napropamide will be ≤0.01 mg/kg in food after a 60 day plant back interval. However the 60 day plantback interval pots also included cabbage seedlings which were not tested. Therefore it is possible residues in food could be higher if this co-planting had not occurred.

Due to crop safety concerns and fate considerations the following replant restrictions (see Vol 1, 3.3.1) have been recommended:

Only supported uses, including brassica vegetable crops and winter oilseed rape, may be drilled/transplanted as following crops. Crops may be drilled only in the following planting season of the next calendar year.

This is supported by the data presented. The details of succeeding crops which may be planted following crop failure and subsequent to a normal harvest will be considered at product evaluation stage. Based purely on rotational crop concerns a plantback interval of 180 days would be recommended; however, although the efficacy and fate recommendation restricts use to the primary crops (brassica vegetables and winter oilseed rape), residues in following crops (even with accumulation) are not expected to significantly exceed the residues found in the primary crops in Section B.7.3.

2.7.8. Summary of other studies

Not applicable.

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

Chronic exposure

The EU MS national TMDIs & NEDIs for the commodities listed below have been calculated using PRIMo – Pesticide Residues Intake Model (revision 2).

The following assumptions have been made:

1) All produce eaten which may have been treated, has been treated and contains residues as given below:

Commodity	**Residue** (mg/kg)
Oilseed rape	0.01
Broccoli, cauliflower, brussels sprout, Head cabbage, chinese cabbage, kale and kohl rabi	0.02

Note the kale, chinese cabbage and kohl rabi uses are not currently supported by residue data.

2) There is no loss of residue during transport or storage, or processing of foods prior to consumption.

The UK NEDIs for the commodities listed above have been calculated for ten consumer groups as detailed in the Regulatory Update 21/2005.

The relevant EU and UK intake estimates are presented in Table 1.1.9-1 and Table 1.1.9-2 respectively.

Chronic intakes for all consumer groups are <1% of the ADI therefore no health effects are expected.

Acute exposure

An assessment of short-term dietary intakes has not been made as napropamide-M is not acutely toxic and an ARfD has not been allocated.

Table 1.1.9-1: EFSA model (PRIMo) for chronic risk assessment

Napropamide-M			
Status of the active substance:		Code no.	
LOQ (mg/kg bw):		proposed LOQ:	
Toxicological end points			
ADI (mg/kg bw/day):	**0.3**	ARfD (mg/kg bw):	**n.n**
Source of ADI:		Source of ARfD:	
Year of evaluation:		Year of evaluation:	

Explain choice of toxicological reference values.

The risk assessment has been performed on the basis of the MRLs collected from Member States in April 2006. For each pesticide/commodity the highest national MRL was identified (proposed temporary MRL = pTMRL).

The pTMRLs have been submitted to EFSA in September 2006.

Chronic risk assessment - refined calculations

TMDI (range) in % of ADI
minimum - maximum

No of diets exceeding ADI: ---

Highest calculated TMDI values in % of ADI	MS Diet	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	pTMRLs at LOQ (in % of ADI)
0.02	PT General population	0.02	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.01	NL child	0.01	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.01	WHO cluster diet D	0.01	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.01	WHO cluster diet E	0.01	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.01	SE general population 90th percentile	0.01	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.01	IE adult	0.01	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.01	FR toddler	0.01	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.01	WHO Cluster diet F	0.00	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.01	WHO regional European diet	0.00	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.00	NL general	0.00	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.00	WHO Cluster diet B	0.00	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.00	UK Infant	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	DE child	0.00	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.00	PL general population	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	FR infant	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	LT adult	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	UK vegetarian	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	UK Toddler	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	UK Adult	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	FR all population	0.00	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.00	DK child	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	DK adult	0.00	Brassica vegetables	0.00	Rape seed		FRUIT (FRESH OR FROZEN)	
0.00	FI adult	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	IT adult	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	ES child	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	ES adult	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
0.00	IT kids/toddler	0.00	Brassica vegetables		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	

Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.

A long-term intake of residues of is unlikely to present a public health concern.

Table 1.1.9-2: UK NEDIs for 10 consumer groups (calculated using chronic consumer version 1.1)

Active substance: Napropamide-M **ADI:** 0.3 mg/kg bw/day **Source:** DAR

	TOTAL INTAKE based on 97.5th percentile									
	ADULT	**INFANT**	**TODDLER**	**4-6 YEARS**	**7-10 YEARS**	**11-14 YEARS**	**15-18 YEARS**	**VEGETARIAN**	**ELDERLY (OWN HOME)**	**ELDERLY (RESIDENTIAL)**
mg/kg bw/day	0.00005	0.00013	0.00012	0.00011	0.00008	0.00006	0.00006	0.00008	0.00006	0.00006
% of ADI	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%

	STMR	**P**	**COMMODITY INTAKES**									
Commodity	**(mg/kg)**		**(mg/kg bw/day)**									
Broccoli	0.02		0.00001	0.00002	0.00003	0.00002	0.00002	0.00001	0.00001	0.00001	0.00002	0.00001
Cauliflower	0.02		0.00002	0.00006	0.00004	0.00003	0.00002	0.00001	0.00002	0.00002	0.00002	0.00001
Brussels sprouts	0.02		0.00001	0.00005	0.00004	0.00003	0.00001	0.00002	0.00001	0.00002	0.00002	0.00001
Head cabbage	0.02		0.00001	0.00004	0.00003	0.00003	0.00001	0.00001	0.00001	0.00002	0.00002	0.00001
Chinese cabbage	0.02		0.00001	L/C	L/C	L/C	L/C	L/C	L/C	0.00001	0.00001	L/C
Kohl Rabi	0.02		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Oilseeds	0.01		0.00003	0.00006	0.00007	0.00007	0.00006	0.00004	0.00004	0.00005	0.00003	0.00004

* 0.00000 corresponds to <0.000005 mg/kg bw/day (any value ≥0.000005 is rounded to 0.00001

L/C Low consumption (<0.1 g/day) or low number of consumers (<4)

2.7.10. Proposed MRLs and compliance with existing MRLs

With respect to MRLs for the proposed use, the data available indicated that the proposed uses would be unlikely to exceed the current MRLs listed in Regulation 396/2005 for napropamide for oilseed rape and brassica vegetables (as shown below).

Code number	Groups and examples of individual products to which the MRLs apply (a)	Napropamide
0240000	. Brassica vegetables (excluding brassica roots and brassica baby leaf crops)	
0241000	. (a) flowering brassica	
0241010	. Broccoli	0.05*
0241020	. Cauliflowers	0.1
0241990	. Others	0.05*
0242000	. (b) head brassica	
0242010	. Brussels sprouts	0.1
0242020	. Head cabbages	0.1
0242990	. Others	0.05*
0243000	. (c) leafy brassica	0.05*
0243010	. Chinese cabbages/pe-tsai	0.05*
0243020	. Kales	0.05*
0243990	. Others	0.05*
0244000	. (d) kohlrabies	0.05*
0400000	. OILSEEDS AND OIL FRUITS	
0401060	. Rapeseeds/canola seeds	0.1

Note the kale, chinese cabbage and kohl rabi uses are not currently supported by residue data.

2.7.11. Proposed import tolerances and compliance with existing import tolerances

Not applicable.

2.8. FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1. Summary of fate and behaviour in soil

Route of degradation in soil

Aerobic soil degradation

Aerobic degradation of radiolabelled [naphthyl-1-^{14}C] napropamide-M was studied in five European soils of contrasting physicochemical properties (range 2.0 -3.7% OM (organic matter); pH 6.6- 7.6) under laboratory conditions. The mass balances varied significantly outside the normal range expected for a radiolabelled study at 75.7 to 154.1% applied radioactivity (AR). Incorrect preparation of the dosing solution and a failure to perform a homogeneity and quantification check may have resulted in individual test vessels receiving different amounts of test substance. The study author normalised the percentage applied radioactivity to percentage recovered radioactivity (% RR).

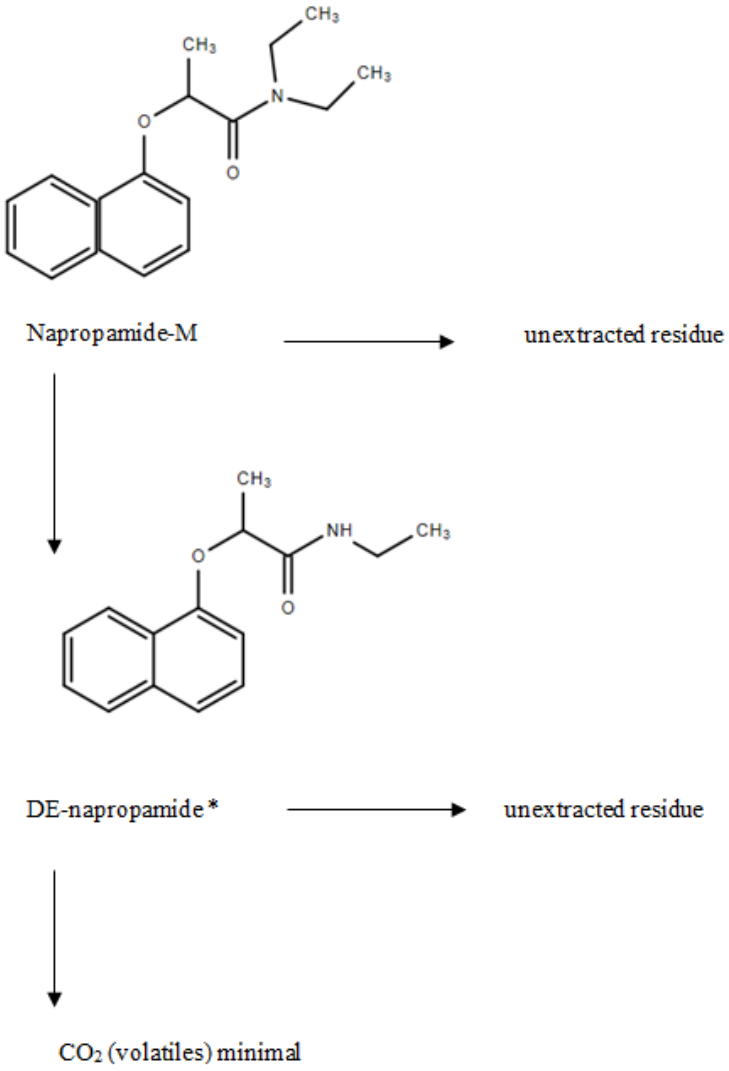
Non-extracted residues (NER) reached a maximum mean 28.4% RR at 120 days but fell by study termination at 180 days (range 5.8- 18.2% mean RR). Mineralisation under laboratory conditions was low as CO_2/volatile levels were reported ≤4% RR across all test soils.

Three minor metabolites were detected: DE-napropamide (maximum mean 8.2% RR) 1,4 naphthoquinone (maximum mean 5.6% RR) and 1-naphthol (maximum mean <1 % RR). All minor metabolites had declined by

study termination at 180 days. No major soil metabolites were formed at ≥10% RR or ≥5% RR at two consecutive time-points under laboratory conditions.

The test facility proposed the following degradation pathway for napropamide-M under aerobic laboratory conditions (figure 2.8.1-1). The Applicant did not provide a degradation scheme in their summary. With very low degradation levels it was difficult to establish a full metabolic soil pathway. The RMS agrees that the proposed scheme gives a good representation of degradation under laboratory conditions as DE-napropamide was the largest of the minor metabolites and was formed in all five soil types.

Figure 2.8.1-1. Test facility's proposed degradation pathway for [naphthyl-1-^{14}C] napropamide-M under laboratory aerobic soil conditions showing minor soil metabolites



*and several other minor metabolites. The true degradation pathway cannot be confirmed but no major metabolites were observed in either laboratory or field soil studies.

Anaerobic soil degradation

Anaerobic soil degradation of radiolabelled [naphthyl-1-^{14}C] napropamide-M was studied in a single clay soil from the UK (3.7% OM; pH 7.3). Mass balances reported (97.2 to 139.6% AR) were outside the range considered acceptable by the OECD guidelines for a radiolabelled study (i.e. 90- 110% AR) due to improper preparation of the dosing solution as explained in the summary for the aerobic study. The results from the study were presented normalised to the total recovered radioactivity (RR) obtained for each replicate sample.
NER reached a maximum mean of 35.7% RR at 121 days before declining to 24.3% RR at 210 days (study termination). CO_2/volatile levels reached a maximum mean of 7.20% RR at day 100. This declined to 6.57% RR at the study end. The RMS assumes that a large proportion of this value was CO_2 but cannot rule out the possibility of an unidentified volatile metabolite.

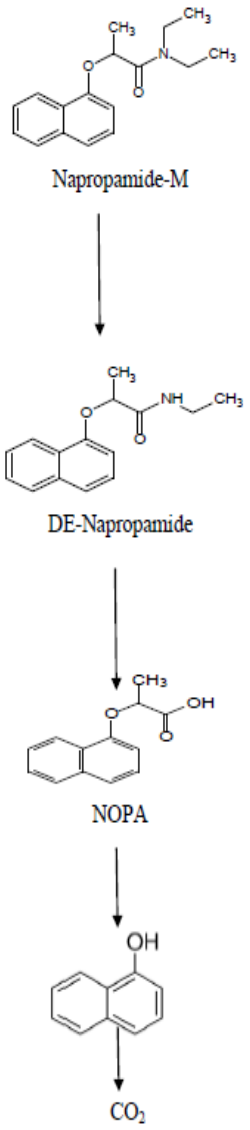
A single minor metabolite DE-napropamide was detected (maximum mean 1.3% RR at day 30 during the aerobic phase). During the anaerobic phase, the maximum mean of 1.2% RR was detected at day 44 before declining to zero at study end. Both the parent compound and minor metabolite were strongly associated with the soil rather than the overlying water. The proposed degradation pathway in figure 2.8.1-1 applies to napropamide-M under anaerobic soil conditions. No novel anaerobic soil metabolites were found.

Photodegradation in soil

Photodegradation of radiolabelled [naphthyl-1-^{14}C] napropamide-M was assessed in a single loam soil from Spain (pH 7.4 and 2.2% OM). NER reached a maximum mean of 8.2% AR at day 18 before declining to 5.4% AR at day 30 (study end). Mineralisation to CO_2 reached a maximum mean of 7.7 % AR at study termination. No CO_2 or volatile substances were observed in the dark control samples.

The metabolites identified in the irradiated samples were DE-napropamide (maximum mean 1.9% AR, 8 day), 1-naphthyl (maximum mean 2.2% AR, 18 day) and NOPA (maximum mean 2.8% AR, 12 day). All metabolites were found <1.0 %AR in the dark samples. The test facility provided the following pathway for photolytic degradation in soil (figure 2.8.1-2)

Figure 2.8.1-2 Test facility's proposed soil photodegradation pathway for [naphthyl-1-^{14}C] napropamide-M under laboratory conditions showing minor photolytic metabolites



All soil laboratory studies investigated the possibility of the isomer napropamide-M (D-form) converting to the L-form. Results from chiral HPLC analysis confirm that napropamide-M remained in the D- form with no indication of isomerisation to the L- form throughout all studies.

Rate of degradation in soil

Aerobic soil degradation

Napropamide-M degraded slowly under aerobic soil laboratory conditions with DT_{50} values ranging from 383-1150 days (n=5; normalised for moisture pF2 and temperature 20 °C). The geometric mean DT_{50} lab was 608 days. The soil DT_{50} lab values were > 60 days and so field dissipation studies were triggered.

A field dissipation study was submitted to meet the requirements of the new EFSA $DegT_{50}$ guidance. The degradation of napropamide-M and one of its metabolites, 2-(1-naphthyloxy) propionic acid (NOPA) was investigated at four European locations (Italy, Spain, Germany and the UK) where both spring and autumn trials were conducted. Application to bare soil was in accordance to the proposed GAP. Persistence endpoints calculated from non-normalised data ranged from overall DT_{50}s of 5.31 to 101.0 days (derived from SFO, FOMC and HS kinetics). A geometric mean $DegT_{50}$ field of 36.24 days is used for the risk assessment. DT_{90} values ranged from 135 to 900 days.

Modelling endpoints, generated using normalised field data (pF2, 20°C) ranged from $DegT_{50}$ 2.82 to 89.6 days (derived from SFO, FOMC and DFOP kinetics). As DFOP kinetics were included in the assessment, a "fast phase" geometric mean $DegT_{50}$ of 14.19 days and a "slow phase" geometric mean $DegT_{50}$ of 28.41 days were generated. Details of how these mean values were applied in groundwater modelling can be found in section 3CP B.8.3. A summary of the persistence and modelling endpoints derived from field studies can be found in table 2.8.1-1 below.

Table 2.8.1-1 RMS summary of persistence and modelling endpoints for the aerobic soil degradation of napropamide-M under field conditions

Trial	Plot	Modelling Endpoints (normalised data)						Persistence Endpoints (non-normalised data)	
		Model	χ^2 err%	Overall $DegT_{50}$	Overall $DegT_{90}$	K1 $DegT_{50}$	K2 $DegT_{50}$	Model	DT_{50} (days)
Italy	Spring	FOMC	14.6	3.34	118	3.34	3.34	FOMC	6.91
	Autumn	SFO modified	16.0	28.6	95.1	28.6	28.6	SFO modified	94.4
Spain	Spring	DFOP * modified	13.5	2.82	630	1.7	440	HS modified	5.31
	Autumn	SFO	16.9	89.6	298	89.6	89.6	HS	101.0
Germany	Spring	SFO modified	14.1	24.0	79.7	24.0	24.0	SFO modified	57.9
	Autumn	SFO	20.2	15.3	50.8	15.3	15.3	SFO	49.0
UK	Spring	SFO	10.7	12.8	42.4	12.8	12.8	SFO	40.7
	Autumn	SFO	7.35	24.0	79.7	24.0	24.0	SFO	73.7
Arithmetic mean				25.06	174.21	24.92	79.71	-	53.62
Geometric mean				15.11	114.15	14.19	28.41	-	36.24

*g value
Kinetic models described as "modified" indicate where an outlier has been removed. Full table can be found at 3CA B.8.1.1.4- 39

NOPA was detected at >LOQ in the 0-10 cm cores in the UK field trial only: three instances in the spring trial (maximum of 0.025 mg/kg at 30 days) and one instance in the autumn trial (0.013 mg/kg at 30 days). Kinetic assessment was not performed for this minor soil metabolite.

Chiral analysis of representative samples from each trial indicated that napropamide-M remained in the D-form with no indication of isomerisation to the L-form.

Anaerobic soil degradation

The anaerobic degradation of napropamide-M in soil under laboratory conditions was very slow and resulted in a DT_{50} of 241 days (SFO kinetics), extrapolated well beyond the study duration.

Photodegradation in soil

The soil photolysis DT_{50} of napropamide-M was calculated as 174 experimental days (SFO kinetics) which is extrapolated beyond the study duration and is therefore uncertain.

Adsorption, desorption and mobility in soil

A batch equilibrium study on the sorption behaviour of radiolabelled [naphthyl-1-^{14}C] napropamide-M was carried out using five test soils (range 1.6- 3.5% OM; pH 6.6-7.8; 5.0- 47.0% clay content). The K_{FOC} values ranged from 313.09 to 746.69 mL/g, (geometric mean 472.61 mL/g) indicating that napropamide-M exhibits low to medium mobility. The Freundlich exponent 1/n, ranged 0.843 to 0.917, with arithmetic mean of 0.865. No pH dependency was observed.

Desorption values for napropamide-M were relatively low across all five soil types, with K_{des1} and K_{des2} values ranging 19.02- 21.26 mL/ g (arithmetic mean) or 16.71- 17.90 mL/g (geometric mean).

There were no major metabolites in soil under laboratory or field conditions, therefore it was not necessary to calculate any adsorption parameters for any metabolites.

Column leaching studies, field leaching studies or lysimeter studies were not submitted for napropamide-M or any of its metabolites, nor were they required.

2.8.2. Summary of fate and behaviour in water and sediment

Route and rate of degradation in aquatic systems

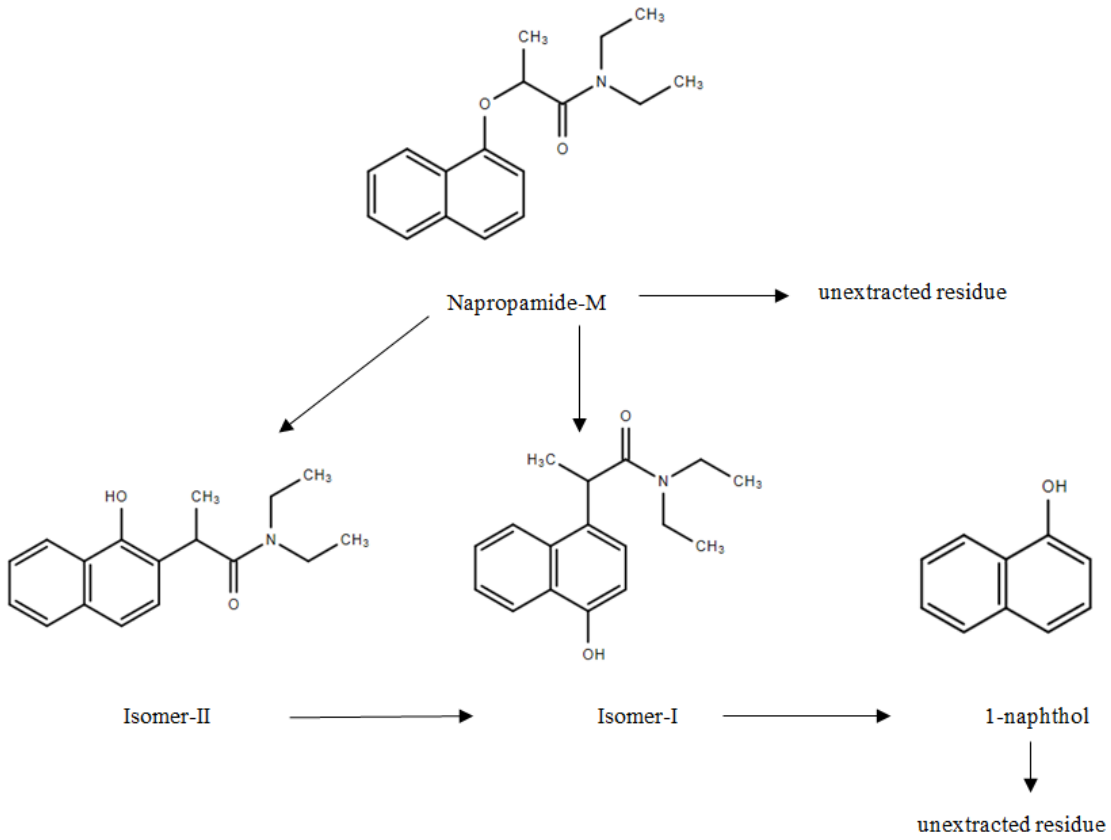
Chemical and photochemical degradation

Radiolabelled [naphthyl-1-^{14}C] napropamide-M was hydrolytically stable at pH 4, 7 and 9 throughout the 10 day study at 50 ±0.5 °C. No major metabolites were observed within the aquatic hydrolysis study and there was no formation of volatiles. As degradation was <10% over the study duration, it is not expected that hydrolytic processes will contribute to the degradation of napropamide-M in the environment.

The direct photodegradation of radiolabelled [naphthyl-1-^{14}C] napropamide-M was studied in a sterile pH 7 buffer. Napropamide-M in irradiated samples degraded completely within the study duration (120 minutes), whereas there was no degradation in the dark controls. Three major photolytic metabolites >10% AR were formed: isomer-I (maximum mean 37.03% AR at 60 minutes), isomer-II (maximum mean 57.1% AR at 30 minutes) and 1-naphthol (maximum mean 23.31% AR at 120 minutes). A minor metabolite present at levels below the LOQ was identified as diethylamine. At the study termination the proportion of applied radioactivity attributed to "other" transformation products was 30.59% AR (mean). The transformation products described collectively as "other" were individually <5% TRR.

The kinetic assessment of the aqueous photolysis study calculated a parent DT_{50} of 6.13 minutes and DT_{50} values for isomer-II, isomer-I and 1-naphthol of 54.5, 75.5 and 90.5 minutes respectively. Figure 2.8.2-1 below shows the degradation pathway used.

Figure 2.8.2-1 RMS aqueous photolysis degradation scheme for napropamide-M



Biological degradation in aquatic systems

Napropamide-M was not considered 'readily biodegradable'.

An 'aerobic mineralisation in surface water' study resulted in <20% degradation of napropamide-M over the study duration (90 days), resulting in uncertain DT_{50} values. Mineralisation to CO_2 accounted for mean values of ≤ 2.4% AR for both test concentrations (1 µg/L and 5 µg/L). Napropamide-M remained fairly constant over the course of the incubation except for the appearance of a possible dimer moiety. The dimer formed a maximum mean concentration of 65.3% AR at day 47 in the higher concentration test solution (5 µg/L). Attempts to identify the dimer were undertaken but could not be confirmed. The study author believes that its formation may be attributed to processes of bacterial dimerization. The Applicant claims this product may have been an artefact formed during sample processing. These claims are unsubstantiated and consequently views from other MS are sought on how to resolve this issue.

The fate and behaviour of radiolabelled [naphthyl-1-^{14}C] napropamide-M was studied in sandy loam (sediment 3.9% OC; water pH 7.4) and clay loam (sediment 5.4% OC; water pH 7.3) water sediment systems under laboratory conditions. Parent rapidly partitioned from the water phase with mean values decreasing from 95.81% AR- 95.10% AR at day 0 to 30.48% AR- 41.50% AR at day 7 over the two systems, with further dissipation of napropamide-M to the sediment phase throughout the study. Non-extracted residues formed a maximum mean 5.99% AR- 12.22% AR at day 60 across the two systems. Mean CO_2 formation was <0.1% AR for both test systems.

No major transformation products were detected in the surface water or the sediment extracts. Two minor metabolites, DE-napropamide and NOPA, were identified in both sandy loam and clay loam systems with mean values all ≤5% AR in both combined and separate water and sediment compartments. Several minor unknown transformation products were detected in both systems. The maximum mean value for unidentified transformation products was 14.09% AR at day 60 in the clay loam system. The RMS can rule out the possibility

of an individual unknown metabolite at ≥5% AR at two consecutive time-points but cannot rule out the possibility of a single unknown metabolite ≥10% AR at this time-point. The Applicant believes that individually none of the unknown degradation products exceeded 10% AR and that one of the day 60 replicates may have been contaminated explaining the high concentration of unknowns for this sample and the lack of any unidentified radioactivity in the corresponding replicate. No evidence to support this claim of contamination was provided.

Table 2.8.2-1 presents the persistence and modelling endpoints resulting from the kinetic reassessment of the water sediment study. Both sets of endpoints are derived at level P-I (parent kinetics level I: one-compartmental approaches).

Table 2.8.2-1 Persistence and modelling endpoints for napropamide-M in water sediment systems

Endpoints	Compartment	Test system	Kinetics	$\chi 2$ error %	DT_{50} (days)	DT_{90} (days)
Persistence[1]	Whole system	Sandy loam	SFO	1.9	301	1000
		Clay loam	SFO	1.43	333	1110
		Arithmetic mean			**317.00**	**1055.00**
		Geometric mean			**316.60**	**1053.57**
	Water phase	Sandy loam	FOMC	4.87	2.96	57.4
		Clay loam	FOMC	5.24	5.53	68.9
		Arithmetic mean			**4.25**	**63.15**
		Geometric mean			**4.05**	**62.89**
Modelling[2]	Water	Sandy loam	SFO	1.9	301	1000
		Clay loam	SFO	1.43	333	1110
		Arithmetic mean			**317.00**	**1055.00**
		Geometric mean			**316.60**	**1053.57**
	Sediment	Sandy loam	**N/A**	N/A	1000 (default)	N/A
		Clay loam	N/A	N/A	1000 (default)	N/A
		Arithmetic mean			**1000**	**N/A**
		Geometric mean			**1000**	**N/A**

[1] Persistence endpoints derived using best fit kinetics at level P-I. A DT50 value for the sediment compartment could not be calculated due to low degradation levels.

[2.] Level P-II kinetic assessment failed. The whole system DegT50 derived at level P-I was assigned to the faster degrading water compartment, whilst a 1000 day default value was assigned to the sediment phase. During modelling for PEC_{SW} and PEC_{SED}, the FOCUS kinetics advice for compounds with K_{OC} between 100 and 2000mL/g was followed: simulations were run with both combinations for ascribing the whole system DT50 and default. The results that give the highest concentrations for the risk assessment were selected.

Degradation in the saturated zone - Water treatment processes

The Applicant provided a reasoned case as to why no substances harmful to human health are expected to arise from napropamide-M via treatment of drinking water (Volume 3 CA Section B.8.2.3.1).

2.8.3. Summary of fate and behaviour in air

The vapour pressure of 3.80 $x10^{-6}$ Pa (25°C), water solubility of 39 mg/l, (20°C) and calculated Henry's law constant of 2.644 $x10^{-5}$ Pa m^3 mol, indicated that napropamide-M exhibits low volatility and has the potential for only very slight volatility from aqueous solutions / soil water.

POP, PBT and vPvB classification

A full detailed POP, PBT and vPvB assessment can be found in Volume 3 CA Section B.8.3.3.

Napropamide-M, although potentially persistent in the environment, particularly in aquatic sediments, is neither bioaccumulative nor susceptible to long range transport; therefore it does not fulfill the criteria for classification as a Persistent Organic Pollutant (POP).

The active substance was considered persistent (P) in the environment under the PBT assessment. The criteria for bioaccumulation (B) and toxicity (T) to the aquatic compartment were not met; therefore the substance is not a PBT substance. Furthermore, napropamide-M is not classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) pursuant to Regulation (EC) No 1272/2008. The active substance is not classified as STOT RE 1 or STOT RE 2 pursuant to Regulation (EC) No 1272/2008.

Although Napropamide-M is potentially very persistent (vP) in the environment, it is not very bioaccumulative (vB) and cannot be considered a vPvB substance

2.8.4. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

Napropamide-M is a new active substance not authorised yet in the EU. Monitoring data are not available or identified as required by this assessment.

2.8.5. Definition of the residues in the environment requiring further assessment

Compartment	Residue/(s)*
Soil	Napropamide-M
Surface Water	Napropamide-M, and metabolites Isomer-I, Isomer-II and 1-naphthol
Sediment	Napropamide-M
Groundwater	Napropamide-M
Air	None

*parent and any metabolites over >10% AR or >5% AR at two consecutive time-points or increasing at study end

2.8.6. Summary of exposure calculations and product assessment

Predicted environmental concentrations in soil

Details of calculations and model inputs can be found in Volume 3 CP Section B.8.2. PEC_{soil} values of napropamide-M were calculated over 5 cm soil depth, (bulk density 1.5 g/cm^3) for a single application of 765 g as/ha. Application to bare soil assuming no crop interception was simulated. The worst-case persistence endpoint, derived from non-normalised field dissipation data was DT_{50} 101 days, determined by HS kinetics. No major soil metabolites were detected in either laboratory or field studies and so none were included in the PEC_{soil} risk assessment.

Proposed GAP uses for napropamide-M are winter oilseed rape and brassicas. The worst case application scenario proposed by the Applicant for the soil risk assessment assumes only one application per year. The RMS notes that for some European locations, it is possible to grow a second brassica crop on the same field within a single year. Therefore it is possible that the same soil could be exposed to two doses within the same year. However, the RMS has proceeded with PEC_{soil} calculations using the Applicant's proposed scenario. This will mean that the risk assessment for soil will be based on and support a single application of 765g napropamide-M per hectare per year.

The maximum initial PEC_{soil} value for napropamide-M is 1.02 mg a.s/kg. This is the case for both proposed GAP crop types.

The maximum DT_{90} from field trials exceeded one year (worst case DT_{90} 900 days, non-normalised), therefore the potential for the accumulation of napropamide-M in soil resulting from consecutive annual applications was considered. The maximum PEC_{soil} accumulation over a 5 cm soil depth, assuming 5 cm tillage was 1.5979 mg/kg.

The PEC_{soil} for the formulated product, D-Devrinol was 2.471 mg/kg.

Predicted environmental concentrations in groundwater

The process undertaken for groundwater modelling is described in detail in Volume 3 CP Section B.8.3. Simulated scenarios were based on the proposed EU GAP of single application of 0.765 kg a.s/ ha SC formulation as a pre-emergence broadcast spray for winter oilseed rape and brassica crops. No major metabolites were observed in any of the soil laboratory or field dissipation studies therefore groundwater modelling was performed with the parent compound only.

The 80th percentile annual average PEC_{GW} for all crop and location scenarios simulated at 1 m soil depth for both PEARL v4.4.4 and PELMO v5.5.3 models were <0.001 µg/l. Simulations using the groundwater model MACRO v.5.5.4 for both proposed GAPs resulted in annual average 80th percentile PEC_{GW} concentrations at 1m depth <0.001 µg/L. PEC_{GW} values for all scenarios generated by all models were at least three orders of magnitude below the regulatory threshold of 0.1 µg/l, demonstrating that the predicted groundwater leaching risk for napropamide-M is negligible.

Predicted environmental concentrations in water and sediment

Modelling for PEC values in surface water and sediment was undertaken for the parent compound napropamide-M and the three major aqueous photolysis metabolites. Full details of the input parameters used in the modelling process are available in section 3CP B.8.5. Applications were simulated to bare soil with no crop interception according to the proposed GAP for winter oilseed rape and brassicas. All scenarios for both crop types exceeded the regulatory acceptable concentration (RAC) of 4.33 µg/L at STEPs 1 and 2.

Modelling at STEP 3 resulted in five out of ten PEC_{SW} values for winter oilseed rape simulations and nine out of fifthteen for brassicas exceeding the RAC. The failing scenarios were driven by drift, drainage or runoff.

Higher tier FOCUS STEP 4 modelling was conducted, simulating buffer zones of 10 m and 20 m to mitigate for spray drift. The failing winter oilseed rape scenarios driven by drift were D3 ditch and D5 stream with PEC_{SW} values of 4.902 and 4.521 µg/L respectively. Both PEC_{SW} values were adequately reduced below the RAC with a 10 m buffer zone to 0.705 and 0.876 µg/L. The three failing brassica scenarios in which the main route of entry to the water body was drift were D3 ditch (1st and 2nd crop) and D6 ditch with PEC_{SW} values of 4.848, 4.853 and 4.747 µgL respectively. The D3 ditch 1st crop value was reduced to 0.697 µg/L with a 10 m buffer. However the other two scenarios were not altered and required a 20 m buffer zone to reduce them below the RAC to 0.362 and 1.837 µg/L.

The main routes of entry to the water body for the remaining failing scenarios were drainage and runoff. The D2 ditch and D2 stream PEC_{SW} values for winter oilseed rape were 23.40 and 14.67 µg/L. Both scenarios were driven by drainage and so could not be mitigated by spray drift buffer zones. Currently, mitigation options for drainflow are limited and are the least developed across the EU. Therefore the RMS did not apply any additional mitigation measures for loadings via drainflow.

One scenario for winter oilseed rape (R3 stream 7.424 µg/L) and six for brassicas (R1, R3 and R4 stream, 1st and 2nd crop, range 4.474- 16.360µg/L) were driven by runoff. The RMS simulated combined mitigation measures of a 20 m spray drift buffer zone and a 10- 12 m vegetative filter strips (VFS) for the runoff scenarios exceeding the RAC. This reduced most of the PEC_{SW} to acceptable concentrations. However, the R3 stream 1st crop and R4 stream 2nd crop PEC_{SW} values remained above the RAC with 6.251 and 7.427 µg/L. The combined measures of a 20 m spray drift buffer and a 18-20 m VFS reduced the R3 stream 1st crop and R4 stream 2nd crop PEC_{SW} values to 3.264 and 3.890 µg/L respectively. The RMS recognises that not all MS accept VFS as a viable, proven mitigation measure. MS will need to consider the appropriateness of this approach for their national authorisations.

The predicted concentrations in surface water at STEPs 3 and 4 for both crop types are reported below. A safe use was demonstrated for most of the FOCUS scenarios for both GAPs proposed. Several scenarios required no mitigation. The maximum 20 m buffer successfully reduced all PEC_{SW} values driven by spray drift below the RAC. All the scenarios driven by runoff were successfully mitigated using either a10-12 m VFS or 18-20 m VFS. However the winter oilseed rape D2 ditch and D2 stream scenarios which were driven by drainage could not be mitigated. These results show that for some European locations where drainflow is the main driver of chemical loading to a water body, environmental concentrations of napropamide-M could present a potentially unacceptable risk to aquatic life (See Volume 1 Section B.9.4.).

The metabolite PEC_{SW} values were calculated from the maximum percentage of each metabolite detected and an adjustment for the difference in molecular weight between parent napropamide-M and each compound. The metabolites were modelled based on the parent PECsw values at STEP 3 and STEP 4. Neither of the metabolites isomer-I or isomer-II exceeded the respective RAC values of 501 or 32 µg/L with or without mitigation measures. No RAC or ecotoxicological data has been provided for the metabolite 1-naphthol. However, the maximum PEC_{SW} for 1-naphthol was below the RAC for the parent compound (4.33 µg/L), which the RMS proposes as a conservative assessment for this metabolite in the absence of specific toxicity data.

Table 2.8.6-1 RMS summary parent STEP 3 and STEP 4 maximum PEC_{SW} for winter oilseed rape

FOCUS Scenario Winter oilseed rape	Application date	No mitigation	Spray drift mitigation		Spray drift and runoff mitigation	Main route of entry into water body
		STEP 3	STEP 4- 10 m BZ	STEP 4- 20 M BZ	STEP 4-20 m BZ + VFS 10-12m	
D2 ditch	8th Sept 86	**23.400**	**23.400**	**23.400**	**23.400**	Drainage
D2 stream	8th Sept 86	**14.670**	**14.670**	**14.670**	**14.67**	Drainage
D3 ditch	26th Aug 92	**4.902**	0.705	0.366	0.366	Drift
D4 pond	27th Aug 85	1.101	1.082	1.072	1.072	Drainage
D4 stream	27th Aug 85	4.190	1.722	1.722	1.722	Drift
D5 pond	13th Sept 78	0.328	0.313	0.305	0.305	Drainage
D5 stream	13th Sept 78	**4.521**	0.876	0.858	0.858	Drift
R1 pond	17th Sept 78	0.1996	0.178	0.167	0.082	Run-off/erosion
R1 stream	17th Sept 78	3.896	3.896	3.896	1.708	Run-off/erosion
R3 stream	22nd Oct 75	**7.424**	**7.424**	**7.424**	3.375	Run-off/erosion

BZ= buffer zone (spraydrift mitigation); VFS= vegetative filter strip (runoff mitigation)
Values in bold indicate PEC_{SW} which exceed the aquatic RAC of 4.33 µg/L

Table 2.8.6-2 RMS summary parent STEP 3 and STEP 4 maximum PEC_{SW} for brassicas

FOCUS Scenario Brassicas	Application date	No mitigation	Spray drift mitigation		Spray drift and runoff mitigation		Main route of entry into water body
		STEP 3	STEP 4-10 m BZ	STEP 4- 20 m BZ	STEP 4-20 m BZ + 10-12m VFS	STEP 4- 20 m BZ + 18-20 m VFS	
D3 ditch 1st	4th May 92	**4.848**	0.697	0.362	0.362	0.362	Drift
D3 ditch 2nd	18th Aug 92	**4.853**	**4.853**	0.362	0.362	0.362	Drift
D4 pond	16th May 85	0.271	0.271	0.261	0.261	0.261	Drainage
D4 stream	16th May 85	3.803	3.803	0.386	0.386	0.386	Drift
D6 ditch	19th Aug 86	**4.747**	**4.747**	1.837	1.837	1.837	Drift
R1 pond 1st	26th Apr 84	0.630	0.630	0.568	0.255	0.15	Runoff/ erosion
R1 pond 2nd	20th Aug 78	0.513	0.496	0.487	0.218	0.127	Runoff/ erosion
R1 stream 1st	26th Apr 84	**6.750**	**6.750**	**6.750**	3.061	1.601	Runoff/ erosion
R1 stream 2nd	20th Aug 78	**6.279**	**6.279**	**6.279**	2.856	1.496	Runoff/ erosion
R2 stream 1st	6th Mar 78	4.190	4.190	3.498	1.555	0.807	Drift
R2 stream 2nd	5th Aug 89	4.297	0.833	0.725	0.433	0.433	Drift
R3 stream 1st	1st Mar 80	**13.820**	**13.820**	**13.820**	**6.251**	3.264	Runoff/ erosion
R3 stream 2nd	15th June 75	**9.024**	**9.024**	**9.024**	4.111	2.158	Runoff/ erosion
R4 stream 1st	5th Mar 84	**4.474**	4.474	**4.474**	2.034	1.066	Runoff/ erosion
R4 stream 2nd	23rd June 85	**16.360**	**16.360**	**16.360**	**7.427**	3.890	Runoff/ erosion

BZ= buffer zone (spray drift mitigation); VFS= vegetative filter strip (runoff mitigation)
Values in bold indicate PEC_{SW} which exceed the aquatic RAC of 4.33 µg/L

Predicted environmental concentrations in air

Volatilisation of napropamide-M from plant or soil surfaces is likely to be low (vapour pressure 3.80 $x10^{-6}$ Pa at 25 °C; Henry's Law constant 2.644 $x10^{-5}$ Pa m^3 mol). Therefore the potential for short-range transport is low. Section 3CA B.8.3.1 details how an atmospheric half-life of 0.046 days (12 hour cycle) was calculated. This falls below the trigger value of DT_{50} ≥2 days indicating that the potential for long-range transport is negligible. Therefore it was not necessary to calculate PEC_{AIR} values.

Other routes of exposure

Not applicable

2.9. EFFECTS ON NON-TARGET SPECIES

EFFECTS ON NON-TARGET SPECIES

2.9.1 Summary of effects on birds and other terrestrial vertebrates

Toxicity to birds: Toxicity data addressing acute and long-term toxicity to birds for the active substance napropamide-M have been provided. For further details of the underlying studies see Volume 3 CA Section B.9. A full list of the available endpoints is provided in the list of endpoints and in the relevant risk assessments for each representative formulation. The following endpoints have been used to perform the risk assessment:

- **Acute toxicity –** A valid study was submitted with napropamide-M, from an acute oral toxicity test with the Japanese quail, *Coturnix coturnix japonica* ([redacted] 2013). The endpoint used in the risk assessment is **LD_{50} > 2000 mg a.s./kg b.w.**
- **Short-term toxicity data -** Under Regulation (EC) 1107/2009 these data are not required and are not used in the risk assessment.
- **Long-term toxicity -** The toxicity estimate used to address the long term risk of the active substance is **NOAEL 309 mg a.s./kg b.w./day** for napropamide racemate, from a one-generation reproduction study with the bobwhite quail (*Colinus virginianus*) ([redacted] 1991).
- **Metabolites** – The RMS considers that the risk from plant metabolites to mammals and birds is acceptable, based on negligible exposure. No endpoints were set and no risk assessment was conducted.
- **Drinking water** - The leaf scenario is not applicable due to the intended use (pre sowing/planting). For the puddle scenario no specific calculations of exposure and TER (Toxicity Exposure Ratios) were necessary since the ratio of effective application rate / NOAEL did not exceed 50.
- **Secondary poisoning -** The Log Pow of napropamide-M is 3.27 therefore consideration of the risk from secondary poisoning is required. The endpoint used in the risk assessment is **LD_{50}/10 = 200 mg a.s./kg b.w** derived from the acute oral toxicity study with the Japanese quail, *Coturnix coturnix japonica* ([redacted] 2013). An assessment of the risk to earthworm eating birds was not required as no relevant soil metabolites were identified (Volume 3 CA B-8). An assessment of the risk to fish eating birds from the relevant metabolites napropamide isomer I and napropamide isomer II was conducted; in the absence of toxicity data, the parent endpoints were used. The LD_{50}/10 of **200 mg/kg bw/d** was used in the risk assessment with a **correction factor of 10** to account for any uncertainty.

Toxicity to mammals: Toxicity data have been provided and considered within the human health assessment (see Volume 3 CA Section B.6 for details of the underlying studies). Endpoints for use in the mammalian risk assessment have been established for acute and long-term toxicity. Bridging of data between napropamide-M and napropamide (racemate) is considered appropriate. The following endpoints have been used in the risk assessment:

- **Acute toxicity –** A valid acute oral toxicity study with the rat was submitted for napropamide-M to address the toxicity of the active substance in the risk assessment, the endpoint used is **LD_{50} >2000 mg a.s./kg b.w** ([redacted] 2010).
- **Long-term toxicity -** A valid three generational study with the rat was submitted for napropamide racemate. The worst case endpoint used to address the risk assessment is **NOAEL = 30 mg a.s./kg b.w. day** ([redacted] 1978).
- **Metabolites –** The RMS considers that the risk from plant metabolites to mammals and birds is acceptable, based on negligible exposure. No endpoints were set and no risk assessment was conducted.
- **Drinking water** - The leaf scenario is not applicable due to the intended use (pre sowing/planting). For the puddle scenario no specific calculations of exposure and TER were necessary since the ratio of effective application rate / NOAEL did not exceed 50.
- **Secondary poisoning -** The Log Pow of napropamide-M is 3.27 therefore consideration of the risk from secondary poisoning is required. The endpoint used in the risk assessment is the long term **NOAEL= 30 mg a.s./kg b.w./day** obtained in the three generational study with the rat' ([redacted] 1978). An assessment of the risk to earthworm eating mammals was not required as no relevant soil metabolites were identified (Volume 3 CA Section B.8). An assessment of the risk to fish eating mammals from the relevant metabolites napropamide isomer I and napropamide isomer II was

conduced, in the absence of toxicity data, the parent endpoints were used. The long-term **NOAEL of 30 mg a.s./kg bw/d** was used in the risk assessment with a **correction factor of 10** to account for any uncertainty.

2.9.2 Summary of effects on aquatic organisms

Tier 1 studies were used to set the endpoints the aquatic compartment. Toxicity data have been provided on D-Devrinol 450 SC, napropamide-M and relevant metabolites. The toxicity data used in the risk assessments are summarised here (Table 2.9.2-1); for further details of the available toxicity data see Volume 3 CA Section B.9. Formulation toxicity data have also been submitted and evaluated (see Volume 3 CP Section B.9).

Table 2.9.2-1 - Summary of endpoints for aquatic organisms

Test substance	Organism	Endpoint	Value	Reference
Fish				
Napropamide-M (Purity 97.2 %)	Rainbow trout *Oncorhynchus mykiss*	96 hr LC_{50}	**11.2 mg a.s/L**	[redacted] 2011a)
Napropamide-M (Purity 96.1 %)	*Zebrafish* (*Danio rerio*)	ELS NOEC	**>0.4 mg a.s/L**	[redacted] (2015)
D-Devrinol 450 SC	Rainbow trout *Oncorhynchus mykiss*	96 hr LC_{50}	30 mg/L 12.3 mg a.s/L	[redacted] (2011b)
Aquatic invertebrates				
Napropamide-M (Purity 97.2 %)	*Daphnia magna*	48 hr EC_{50}	**19 mg a.s/L**	Liedtke, A (2011c)
Napropamide-M (Purity 96.14 % D-isomer, 3.86 % of L-isomer)	*Daphnia magna*	21-day NOEC	**0.3 mg a.s/L**	Kamile, M.K (2014)
D-Devrinol 450 SC	*Daphnia magna*	48 hr EC_{50}	52 mg/L 21.32 mg a.s/L	Liedtke, A (2011d)
Algae				
Napropamide-M (Purity 97.26 % D-isomer, 3.86 % L-isomer)	*Pseudokirchneriella subcapitata*	72 hr E_rC_{50}	28.18 mg a.s/L NOEC 0.8 mg a.s/L	Kamile, M.K (2014) X
Napropamide (Purity 93.2%)	*Anabaena* sp.	72h E_rC_{50}	55.0 mg a.s./L	Jenkins, (2002)
D-Devrinol 450 SC	*Pseudokirchneriella subcapitata*	72 hr E_rC_{50} NOEC	**30 mg/L** [a] **>12.45 mg a.s/L**[a] 0.09 mg/L 0.037 mg a.s./L	Kamle, M (2014)

Test substance	Organism	Endpoint	Value	Reference
Aquatic macrophytes				
Napropamide-M (Purity 96.1 %)	*Lemna gibba*	7-day E_rC_{50}	**0.08 mg a.s./L**	Ramsden, C (2015)
Isomer I	*Lemna minor*	7-day E_yC_{50} 7-day E_rC_{50}	0.729 mg a.s./L † **>5.81 mg a.s/L**	Juckeland, 2012a
Isomer II	*Lemna minor*	7-day E_yC_{50} 7-day E_rC_{50}	0.603 mg a.s./L † **>0.321 mg a.s/L**	Juckeland, 2012b
Napropamide-M	*Myriophyllum spicatum*	14 day E_rC_{50}	2.35 mg a.s/L	Hermes, H (2015)
D-Devrinol 450 SC	*Lemna gibba*	7-day E_rC_{50} NOEC	0.096 mg/L **0.0443 mg a.s/L** 0.004 mg/L 0.001 mg a.s./L	Ramsden, C (2015)

[a] As effects of >50 % were not reported in the study, an extrapolated E_rC_{50} was calculated using regression analysis to be 69.43 mg product/L (equivalent to 28.81 mg a.s/L) however to provide a conservative assessment the maximum concentration tested of 30 mg product/L (equivalent to 12.45 mg a.s/L) is used in the risk assessment.
† Endpoint not used in risk assessment provided for information only.
X Study not considered suitable for risk assessment.
Bold-values have been used in the risk assessment.

The tier 1 studies identified aquatic macrophytes as the most sensitive aquatic organisms with ErC_{50} (EC_{50} in terms of reduction of growth rate) values of 0.08 mg a.s./L (napropamide-M) and 0.0443 mg a.s/L (D-Devrinol 450 SC).

There is negligible difference between the formulation and active substance endpoints for fish and aquatic invertebrates (fish: LC_{50}=11.2 (a.s.) and 12.3 mg a.s/L (formulation); aquatic invertebrates: EC_{50}=19 mg a.s/L (a.s.) and EC_{50}=21.32 mg a.s/L (formulation)). Therefore the lower is used in the FOCUS assessment. For algae the study with the active substance was found to be unreliable therefore the formulation endpoint (>12.45 mg a.s/L) is used in the risk assessment. For aquatic macrophytes the formulation and active substance endpoints are considered equivalent (ErC_{50}=0.08 mg a.s/L (a.s.) and ErC_{50}=0.0443 mg a.s/L (formulation)) as they are within a factor of two (EFSA Journal 2013;11(7):3290). Therefore the lower of the two is used in the FOCUS risk assessment. As the active substance and formulation endpoints are considered equivalent, no separate spray drift assessment is required for the formulation as the risk will be addressed in the active substance FOCUS assessment.

2.9.3 Summary of effects on arthropods

Toxicity to Bees: Toxicity data has been provided to address the acute toxicity to bees from D-Devrinol 450 SC. Oral and contact studies in bees identified LD_{50} values greater than the top dose tested. Data for napropamide-M have not been provided and instead the toxicity data for D-Devrinol 450 SC are used. The following endpoints have been used to perform the risk assessment:

- **Acute oral toxicity –** A valid study was submitted with D-Devrinol 450 SC (Rana, J.R 2014a). The endpoint used in the risk assessment is **LD_{50} > 110 µg a.s/bee.**
- **Acute contact toxicity -** A valid study was submitted with D-Devrinol 450 SC (Rana, J.R 2014b). The endpoint used in the risk assessment is **LD_{50} > 110 µg a.s/bee.**

Toxicity to arthropods: For non-target arthropods, tier 1 residue contact tests were submitted to address the acute toxicity to arthropods form D-Devrinol 450 SC for the two indicator species *Aphidius rhopalosiphi* and *Typhlodromus pyri.* The following endpoints have been used to perform the risk assessment:

- ***Aphidius rhopalosiphi*** - A valid study was submitted with D-Devrinol 450 SC (Gamblin, C. 2014). The endpoint used in the risk assessment is **LR_{50} (lethal rate that causes 50% mortality) > 9 L/ha (equivalent to >4140 g a.s/ha**).
- ***Typhlodromus pyri*** - A valid study was submitted with D-Devrinol 450 SC (Cockroft, R. 2014). The endpoint used in the risk assessment is **LR_{50} > 9 L/ha (equivalent to >4140 g a.s/ha**).

No statistically significant sublethal effects on reproduction were observed for either species.

2.9.4 Summary of effects on non-target soil meso- and macrofauna

Toxicity to the earthworm: Toxicity data have been provided to address the chronic toxicity to the earthworm (*Eisenia foetida)* from D-Devrinol 450 SC. An assessment of the acute risk is no longer required in accordance with SANCO/11803/2010 guidance. The following endpoint has been used to perform the risk assessment:

- ***Eisenia foetida*** - A valid study was submitted with D-Devrinol 450 SC (Rana J.R (014c). The endpoint used in the risk assessment is **NOEC = 17.3 mg a.s/kg soil** (equivalent to 83.4 mg formulation/kg artificial soil).

Toxicity to other non-target soil meso- and macrofauna : Toxicity data have been provided for napropamide-M to address the chronic toxicity to the Predatory mite (*Hypoaspis aculeifer)* and the Springtail (*Folsomia candida).* The following endpoints have been used to perform the risk assessment:

- ***Hypoaspis aculeifer*** - A valid study with napropamide-M (Vinall, S. 2014) was submitted. The endpoint used in the risk assessment is **NOEC >500 mg a.s/kg soil**.
- ***Folsomia candida*** - A valid study with napropamide-M (Vinall, S. 2014) was submitted. The endpoint used in the risk assessment is **NOEC >47.7 mg a.s/kg soil**.

2.9.5 Summary of effects on soil nitrogen transformation

Nitrogen transformation: Toxicity data have been provided for D-Devrinol 450 SC to address the effects on soil nitrogen transformation. The following endpoint has been used to perform the risk assessment:

- ***Soil microorganisms*** - A valid study with D-Devrinol 450 SC (Shrimali A. 2013) was submitted. The endpoint used in the risk assessment is **NOEC = 32 mg a.s/L.** The effects of D-Devrinol on nitrogen transformation were found to be within ± 25% of the control levels.

2.9.6 Summary of effects on terrestrial non-target higher plants

Toxicity to non-target higher plants: Toxicity data have been provided to address the toxicity to non-target plants from D-Devrinol 450 SC. The following endpoints have been used in the risk assessment:

Seedling emergence - A valid study with D-Devrinol 450 SC was provided in which Ryegrass (*Lolium perenne)* was identified to be the most sensitive species. The endpoint is **ER_{50} (effective application rate) = 76.6 g a.s./ha (**R.A. Dickinson 2014a).

Vegetative vigour – A valid study with D-Devrinol 450 SC was provided in which Oat (*Avena sativa)* was identified to be the most sensitive species. The endpoint is **ER_{50} = 521 g a.s./ha**' (R.A. Dickinson 2014b).

2.9.7 Summary of effects on other terrestrial organisms (flora and fauna)

No other data on the effects of napropamide-M, D-Devrinol 450 SC or metabolites on other terrestrial organisms are available. As acceptable risk has been shown for all the standard test organisms, further testing on additional species is not considered necessary.

2.9.8 Summary of effects on biological methods for sewage treatment

Activated sludge - A valid study with napropamide racemate (Hertl, J 2003), in which an endpoint of **EC_{50} (Half maximal effective concentration) > 1000 mg a.s./L** was obtained, was provided. The effects on biological activity of sewage sludge were not detected at concentrations up to and including 1000 mg a.s./L.

2.9.9 Summary of product exposure and risk assessment

B.9.2.1 Risk assessment for Birds

The results of the risk assessment is summarised here. The risk assessment was conducted according to EFSA (2009) 'Guidance document on risk assessment for birds & mammals'..

When applied in accordance with the proposed GAP in the product D-Devrinol 450 SC, the active substance napropamide-M has demonstrated acceptable acute (TER_A = 105) and reproductive risk (TER_{LT} = 43) to birds at the screening step.

The risk to birds via secondary poisoning (risk to fish-eating birds (TER_{fish}=547.9), risk to earthworm-eating birds (TERworm =35.2)) was also found to be acceptable. For the metabolites napropamide isomer I and napropamide isomer II the risk to fish eating birds was considered to be acceptable (TER for both = 54.79). No assessment was required for the risk to earthworm eating birds in relation to metabolites.

B.9.2.2 Risk assessment for Mammals

The results of the risk assessment is summarised here. Risk assessments were conducted according to EFSA (2009) 'Guidance document on risk assessment for birds & mammals'.

When applied in accordance with the proposed GAP in the product D-Devrinol 450 SC, the active substance napropamide-M has demonstrated acceptable acute (TER_A = 181) and reproductive risk (TER_{LT} = 11) to mammals at the screening step.

The risk to mammals via secondary poisoning (risk to fish-eating mammals (TER_{fish}=92.3), risk to earthworm-eating mammals (TERworm =6.1)) was also found to be acceptable. For the metabolites napropamide isomer I and napropamide isomer II the risk to fish eating mammals was considered to be acceptable (TER for both = 9.375). No assessment was required for the risk to earthworm eating mammals in relation to metabolites.

B.9.4 Risk assessment for Aquatic organisms

The risk assessment included in Volume 3 CP Section B.9.4. indicated an acceptable risk to aquatic organisms from the active substance, metabolites and formulation providing mitigation is considered. The results of the risk assessment is summarised here. Risk assessments were conducted according to EFSA (2013) guidance "Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters".

Surface water

A comparison of the toxicity of the formulation and active substance identified that the active substance and formulation endpoints are equivalent, therefore no separate spray drift assessment is required for the formulation as the risk will be addressed in the active substance FOCUS assessment.

For fish and aquatic invertebrates, acceptable acute and chronic risk has been demonstrated at FOCUS step 3 for all scenarios. For Algae an acceptable risk has been demonstrated at FOCUS step 3 for all scenarios.

For aquatic macrophytes, at FOCUS Step 4 the risk was unresolved for the scenarios D2 Ditch and D2 stream for Winter oilseed rape, based on a regulatory acceptable concentration (RAC) of 4.33 µg a.s./L with a 20 meter buffer zone and vegetative filter strips considered. It is also noted that the addition of the vegetative filter strips successfully resolved the risk for the relevant scenarios for Winter oilseed rape (R3 Stream) and Brassica vegetable crops (R1 Stream 1st, R1 Stream 2nd, R3 stream 2nd, R4 stream 1st and R3 Stream 1st and R4 Stream 2nd) however this method is not accepted as a viable mitigation measure in all Member States. The relevance of this should also be considered further at the Member State level. This assessment is driven by the risk to aquatic macrophytes (*Lemna gibba*).

Metabolites

The following metabolites were identified as relevant in surface waters: Isomer I, napropamide Isomer II and Naphthanle-1-ol. An assessment at FOCUS step three identified acceptable risks for all organisms and all crop scenarios; further consideration is not required.

An acceptable acute and chronic risk has been demonstrated for napropamide Isomer I, napropamide Isomer II and Naphthanle-1-ol for fish, aquatic invertebrates, algae and aquatic macrophytes.

Groundwater

Groundwater PEC values were <0.001 µg/L for all GAP uses and the relevant metabolites (see Volume 3 CA Section B.8), therefore a low risk to aquatic organisms from napropamide-M and relevant metabolites was estimated for groundwater. It is considered that the risk has been sufficiently addressed in the surface water risk assessment.

B.9.6.1 Risk assessment for Bees

The risk assessment included in Volume 3 CP section B.9.6.1 indicated an acceptable risk to bees for the formulation and the active substance. The risk assessment was conducted according to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002). The first tier risk assessment indicated an acceptable risk to *Apis melifera* from the formulation based on the proposed use. The Hazard Quotient (HQ) for both oral and contact exposure was ≤ 7. As all HQ values were below the relevant trigger value an acceptable risk was concluded.

The applicant has not provided oral or contact toxicity studies with the active substance, napropamide-M. It was concluded that in this case it is acceptable to assume that the majority of the toxicity to bees from D-Devrinol 450 SC is attributed to the active substance. For further details please refer to Volume 3 CP Section B.9.6.1.

B.9.6.2 Risk assessment for Non-target arthropods

The risk assessment included in Volume 3 CP Section B.9.6.2 indicated an acceptable risk to non-target arthropods from the formulation. The risk assessment was conducted according to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002).

In-field risk - The first tier risk assessment indicated an acceptable risk to both *Aphidius rhopalosiphi* (HQ = <0.18) and *Typhlodromus pyri* (HQ = <0.18).

Off-field risk - The first tier risk assessment indicated an acceptable risk to both *Aphidius rhopalosiphi* (HQ = <0.0051) and *Typhlodromus pyri* (HQ = <0.0051).

Therefore, an acceptable risk to non-target arthropods was identified for the proposed use.

B.9.8.1 Risk assessment for Earthworms

The risk assessment included in Volume 3 CP Section B.9.8.3 indicated an acceptable risk to earthworms from the formulation. The risk assessment was conducted according to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002).

The risk assessment of chronic toxicity to earthworms resulted in a TER of 10.95 at an accumulation PEC_{soil} of 1.5795 mg a.s./kg soil d.w., which is greater than the trigger of five. An acceptable risk was therefore identified for the proposed use of the product.

B.9.8.2 Risk assessment for other non-target soil meso- and macrofauna

The risk assessment included in Volume 3 CP Section B.9.8.4 indicated an acceptable risk to other soil meso- and macrofauna. The risk assessment was conducted according to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002).

The lowest TER for the representative species *Folsomia candida* and *Hypoaspis aculeifer* was 30.20, compared to a trigger of five. This was calculated based on comparison to the single proposed use and the accumulation PEC of 1.5795 mg a.s/kg soil. An acceptable risk to non-target soil meso- and macrofauna was therefore identified.

B.9.10 Risk assessment for effects on soil nitrogen transformation

The risk assessment included in Volume 3 CP Section B.9.10 indicated an acceptable risk to soil nitrogen transformation processes from the formulation. The risk assessment was conducted according to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002).

When the active substance is tested with the representative formulation (D-Devrinol 450 SC) at a treatment rate of 32.40 mg a.s./kg soil d.w. a 7.79 % effect on nitrogen transformation rates was observed. The test rate was 20 times the accumulation PEC_{soil} (1.5795 mg a.s./kg soil d.w.) and within the acceptable range of ± 25 % effects. This result indicates that an acceptable risk to soil nitrogen transformation processes based on the proposed use of the representative formulation has been identified.

B.9.12. Risk assessment for terrestrial non-target higher plants

The risk assessment included in Volume 3 CP Section B.9.12.1 indicated an acceptable risk to non-target plants providing a 5 meter buffer zone is considered. The risk assessment was conducted according to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002).

For vegetative vigour an acceptable tier 1 risk was identified with no mitigation required (TER=25). For seedling emergence an acceptable risk could not be identified initially (TER=3.6) and further consideration of the risk was required. It was determined that an acceptable risk can be identified with the implementation of a 5 meter buffer zone (TER=17.56).

B.9.13 Risk assessment for other terrestrial organisms (flora and fauna)

No other terrestrial organisms were considered during the risk assessment.

B.9.14 Risk assessment for biological methods for sewage treatment

The risk assessment included in Volume 3 CP Section B.9.14.1 indicated an acceptable risk to sewage treatment processes. The EC_{50} calculated in the submitted activated sewage sludge test was ≥ 1000 mg a.s./L, and exceeds the limit of solubility for the active substance. This information indicates that an acceptable risk to sewage treatment processes can be identified. No Member State issues were identified.

2.10. CLASSIFICATION AND LABELLING

Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	-	-	-	Data conclusive but not sufficient for classification
2.2.	Flammable gases	-	-	-	Hazard class not applicable (solid)
2.3.	Flammable aerosols	-	-	-	Hazard class not applicable (solid)
2.4.	Oxidising gases	-	-	-	Hazard class not applicable (solid)
2.5.	Gases under pressure	-	-	-	Hazard class not applicable (solid)
2.6.	Flammable liquids	-	-	-	Hazard class not applicable (solid)
2.7.	Flammable solids	-	-	-	Data conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	-	-	-	Data conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	-	-	-	Hazard class not applicable (solid)
2.10.	Pyrophoric solids	-	-	-	Data conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	-	-	-	Data conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	Data conclusive but not sufficient for classification
2.13.	Oxidising liquids	-	-	-	Hazard class not applicable (solid)
2.14.	Oxidising solids	-	-	-	Data conclusive but not sufficient for classification
2.15.	Organic peroxides	-	-	-	Data conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	-	-	-	Hazard class not applicable
3.1.	Acute toxicity – oral	-	-	-	Data conclusive but not sufficient for classification
	Acute toxicity – dermal	-	-	-	Data conclusive but not sufficient for classification

	Acute toxicity - inhalation	-	-	-	Data conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	-	-	-	Data conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	-	-	-	Data conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	-	-	-	Data lacking
3.4.	Skin sensitization	-	-	-	Data conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	-	-	-	Data conclusive but not sufficient for classification
3.6.	Carcinogenicity	-	-	-	Data conclusive but not sufficient for classification
3.7.	Reproductive toxicity	-	-	-	Data conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	-	-	-	Data conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	-	-	-	Data conclusive but not sufficient for classification
3.10.	Aspiration hazard	-	-	-	Hazard class not applicable (solid)
4.1.	Hazardous to the aquatic environment	H410: Very toxic to aquatic life with long lasting effects	10 acute; 10 chronic	-	-
5.1.	Hazardous to the ozone layer	-	-	-	Hazard class not applicable

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

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

Provisional Hazard Classification/Labelling of plant protection products according to Regulation (EC) 1272/2008

Pictogram: GHS09
Signal word: Warning
Hazard statements: H410: Very toxic to aquatic life with long lasting effects.
M-factor: 10 acute; 10 chronic

Justification for classification according to Regulation (EC)1272/2008:

Acute category:

Active substance

The lowest acute toxicity endpoint for the active substance is an E_rC_{50} of 0.08 mg a.s./L for toxicity to aquatic macrophytes' (fish LC_{50} 11.2 mg a.s./L, aquatic invertebrate EC_{50} 19 mg a.s./L and algae ErC_{50} of 12 45 mg/L). As this is <1 mg/L, acute category 1 applies to the active substance.

Formulation

The lowest acute toxicity endpoint for the formulated product is an E_rC_{50} of 0.096 mg/L for toxicity for aquatic macrophytes (fish LC_{50} 30 mg/L, aquatic invertebrate EC_{50} 52 mg/L and algae E_rC_{50} 30 mg/L). As this is <1 mg/L, acute category 1 applies to the formulated product.

Chronic category:

Active substance

The lowest chronic toxicity endpoint for the active substance is an NOEC (EC_{10} value taken as true NOEC could not be determined) of 0.003 mg a.s/L for toxicity to aquatic macrophytes (fish NOEC >0.4 mg a.s/L, aquatic invertebrate NOEC 0.3 mg a.s./L and algae NOEC 0.8 mg a.s./L). As this is <0.1 mg/L and the substance is not rapidly degradable, chronic category 1 applies to the active substance.

Formulation

The chronic toxicity endpoints for aquatic macrophytes (NOEC 0.004 mg/L) and algae (NOEC 0.09 mg/L) are the only chronic endpoints considered for the formulation, therefore they been used for classification. The substance is not 'rapidly biodegradable' and as the NOEC for aquatic macrophytes is below the critical value of 0.1, the formulated product is classified as chronic category 1.

In order to determine the chronic classification for fish and aquatic invertebrates for the formulation, active substance endpoints have been used for extrapolation. The fish and aquatic invertebrate NOECs are >0.4 mg a.s/L and 0.3 mg a.s/L, respectively. The active is therefore classified as chronic category 2 based on these species and the assumption of 'not' readily biodegradable (>0.1 to <1 mg/L).

The formulated product D-Devrinol 450 SC contains 41.49% w/w napropamide-M. The CLP guidance states that for components classified as 'Chronic 2, Chronic 3 or Chronic 4' the relevant concentration is 1% w/w or greater, therefore napropamide-M (41.49% w/w) is considered to be a relevant component. No Chronic endpoint is required.

- Summation method

w/w of 'chronic category 2'=≥25% then classified as chronic category 2.

= 41.49 therefore chronic category 2.

The summation method determined chronic category 2 for the active substance extrapolation. As the classification for the formulation based on the aquatic macrophytes endpoint (0.004 mg/L) was determined to be chronic category 1, this will be retained as it is worst case.

GHS09 Pictogram	Required for 'aquatic acute category 1' and 'aquatic chronic category 1'
Signal word 'Warning'	Required for 'aquatic acute category 1' and 'aquatic chronic category 1'
P273, P 391, P 501	Required for 'aquatic acute category 1' and 'aquatic chronic category 1'

2.11. RELEVANCE OF METABOLITES IN GROUNDWATER

There were no significant metabolites detected in the soil degradation studies. All observed metabolites were <10% or <5% on two consecutive sampling occasions. Therefor there were no potentially relevant metabolites that needed to be considered with respect to groundwater.

2.12. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

For details on the D : L isomeric ratio found in napropamide-M active substance as manufactured, refer to the confidential Volume 4. There is no impact of the isomeric composition of napropamide-M on any area of the risk assessment.

2.12.1. Identity and physical chemical properties

No impact on risk assessment.

2.12.2. Methods of analysis

No impact on risk assessment. Methods are available to determine isomer ratio (in technical material and formulated product) as required. A specific method of analysis for napropamide-M (D isomer) in the formulated product is available and suitably validated.

2.12.3. Mammalian toxicity

No impact on risk assessment. There was no evidence that the isomer ratio was altered in mammalian systems. The toxicological properties of napropamide-M are comparable with those of napropamide (racemate).

2.12.4. Operator, Worker, Bystander and Resident exposure

No impact on risk assessment. The proposed end-points for risk assessment are not impacted by isomeric composition.

2.12.5. Residues and Consumer risk assessment

The metabolism of napropamide-M has been investigated in oilseed rape. The previously evaluated metabolism studies for napropamide were also considered (cabbage, tomatoes, apples, potatoes, oilseed rape). Considering the low levels of residues found in rapeseed, and the margin of safety shown in the consumer risk assessment, additional studies to elucidate further potential differences in napropamide and napropamide-M metabolism are not considered warranted. Therefore, no impact on risk assessment.

2.12.6. Environmental fate

All environmental fate and behaviour studies were performed using the resolved isomer, napropamide-M as the test substance. The supplied test material was reported as 99.9% of the desired isomer (D-form). Chiral HPLC analysis was undertaken for all studies. The RMS has confirmed that napropamide-M remained as the D-isomer throughout all environmental fate studies and no isomerisation to the L-form occurred. Therefore o impact on risk assessment.

2.12.7. Ecotoxciology

The following batches were used in the ecotoxicological evaluation of napropamide-M: UPH-08/DNE-263/Tech/20121226 and Batch UPV/714-181/DEV/014. Analysis confirmed that these two batches were 96.15% and 99.5% of the D-isomer form respectivly and were considered equivelent to the proposed specification of napropamide-M (volume 4). Therefore, no impact on risk assessment.

2.13. RESIDUE DEFINITIONS

2.13.1. Definition of residues for exposure/risk assessment

Food of plant origin: napropamide (sum of the R- and S- isomers at any ratio)

Food of animal origin: Not required - residues intakes by livestock are <0.004 mg/kg bw/day

Soil: napropamide-M

Groundwater: napropamide-M

Surface water: napropamide-M and metabolites isomer-I, isomer-II and 1-naphthol

Sediment: napropamide-M

Air: napropamide-M

2.13.2. Definition of residues for monitoring

Food of plant origin: napropamide (sum of the R- and S- isomers at any ratio)

Food of animal origin: Not required residues intakes by livestock are <0.004 mg/kg bw/day

Soil: Not required

Groundwater: Not required

Surface water: Not required

Sediment: Not required

Air: Not required

Environmental residue definition for enforcement purposes to be confirmed after expert peer review.

Level 3

Napropamide-M

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

3.1.1.1. 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.	X		It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with for napropamide-M for use as a herbicide on winter oilseed rape, flowering brassicas and head brassicas crops (refer to Level 1, Table 1.5.1 for details of the representative use considered D-Devrinol).
3.1.1.2. Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted		X	Date gaps have been identified (see Level 3.1.4)
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		The identified data gaps at Level 3.1.4 are considered to be confirmatory in nature.
3.1.1.3. 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		*(a) the minimum degree of purity of the active substance;* 930 g/kg (napropamide-M, D-isomer) 965 g/kg (napropamide-M, sum of D-isomer and L- isomer) *(b) the nature and maximum content of certain impurities;* There are no impurities or by-products of particular environmental or toxicological concern. There are no proposed relevant impurities. *(c) restrictions arising from the evaluation of the information referred to in Article 8 of 1107/2009 taking account of the agricultural, plant health and environmental, including climatic, conditions in question;*

				n/a *(d) type of preparation;* n/a *(e) manner and conditions of application;* n/a *(f) submission of further confirmatory information to Member States, the Commission and the European Food Safety Authority, (the Authority), where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge;* n/a *(g) designation of categories of users, such as professional and non-professional;* n/a *(h) designation of areas where the use of plant protection products, including soil treatment products, containing the active substance may not be authorised or where the use may be authorised under specific conditions;* n/a *(i) the need to impose risk mitigation measures and monitoring after use;* Member States should consider: - The risk to aquatic organisms and in particular the need for risk mitigation in the form of buffer zones and/or vegetated filter strips - The risk to terrestrial non-target plants and in particular the need for risk mitigation in the form of buffer zones *(j) any other particular conditions that result from the evaluation of information made available in the context of Regulation 1107/2009.* Member States should consider: - Only supported uses, including brassica vegetable crops and winter oilseed rape, may be drilled/transplanted as following crops. Crops may be drilled only in the following planting season of the next calendar year. The details of succeeding crops which may be planted following crop failure and subsequent to a normal harvest will be considered at product evaluation stage.
3.1.1.4. Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to	X		The data submitted are sufficient to establish an Acceptable Daily Intake (ADI), an

	establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).			Acceptable Operator Exposure Level (AOEL) and an Acute Reference Dose (ARfD) when necessary.
	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.	X		Sufficient plant metabolism and trial data have been provided to demonstrate that residues from the proposed uses on flowering brassicas, head brassicas and oilseed rape are below the LOQ. Exceedances of current MRLs are not expected. Additional residue trial data are required to support uses on leafy brassicas and kohl rabi (see SANCO/7525/VI/95 rev.10.2). Due to the low residues in plants data on the nature and magnitude of residues in processed products and products of animal origin are not required. Residues in succeeding crops are expected to be below LOQ with a 180 days plantback interval. This interval is covered by a crop saftety restriction proposed in 3.3.1. No risk to the consumer resulting from the presence of napropamide-M residues in plant commodities for the GAPs proposed has been identified.
	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.	X		This is considered to apply to the representative use examined.
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		At least one representative formulation is proposed and a GAP with the maximum field rate and a summary of effectiveness and crop safety was provided. Data were provided to the appropriate EPPO standards, and GEP certificates are available and will be further examined at the product authorisation stage. It is considered that the data provided here are sufficient to establish that the active substance is sufficiently effective and has no unacceptable effects on the plants or their yield.
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or	X		Sufficient information has been presented by UPL Europe Ltd to permit the establishment of the toxicological, ecotoxicological and environmental relevance

	environmental relevance of metabolites.			of metabolites.
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		Five batch analyses data generated using representative full scale production material supporting the proposed specification are included in the confidential section (Vol 4). The approach to method validation, incluing isomer ratio/determination, to support the specification is discussed in vol 4 (confidential section); the validation data are considered adequate to support the specification. The specification is considered supported by the batch analytical data which is based on full scale production batches. <u>Ecotoxicology</u> Yes – with reference to Volume 4, it is considered that the relevant batches of napropamide-M (Batch UPV/714-181/DEV/014 and UPH-08/DNE-263/Tech/20121226) are equivelent to the technical specification. It is noted that for napropamide detailed analysis of the batch content has not been conducted and information on the identity and levels of specific impurities in these batches is not available. <u>Tox</u> Yes; as stated under 'Ecotoxicology', above. <u>Environmental fate</u> Yes- with reference to volume 4, the relevant batches of napropamide-M used in the environmental fate and behaviour studies can be considered equivalent to the technical specification.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	-		There is no FAO specification for napropamide-M or napropamide
	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	-		There is no FAO specification for napropamide-M or napropamide
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of	X		Fully acceptable validated methods of analysis are available for 'total napropamide' content and also stated impurities in the proposed specification.

	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.			A chiral method of analysis has been used to derive an isomer ratio (napropamide-M (D-isomer) and L isomer for each batch, and this method was considered to be adequately validated to support the proposed specification. See the Volume 4 (confidential section) and section B.5.1 for further information.
	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		The information submitted with regards to methods of analysis is sufficient to support approval. Refer also to Level 2.5
	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		Refer to level 2.5 for further details.
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		Reference doses (ADI and AOEL) can be established from the available toxicological studies. These are derived from NOAELs identified from standard regulatory studies, with the application of a standard safety margin of 100. The available toxicological studies (see section 2.6) indicate that an ARfD is not required.
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	A full dataset of *in vitro* and *in vivo* toxicity studies has been conducted, in which the active substance was applied at limit or cytotoxic concentrations. Although the active substance is positive in vitro in a mammalian gene mutation assay, a valid negative result was obtained in an *in vivo* comet assay. It is therefore concluded that the active substance does not demonstrate any genotoxic potential *in vivo*. Napropamide-M does not meet the criteria for classification for germ cell mutagenicity.
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		X	The long-term toxicity and carcinogenicity potential of the active substance has been investigated in rats and mice. There was no evidence of a treatment-related increase in tumours in either species. It is proposed that napropamide-M should not

	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.**			be classified for carcinogenicity.
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.	n/a	n/a	Not applicable as napropamide-M is not considered to be a carcinogen.
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 classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**		X	The reproductive toxicity of the active substance has been investigated in a three-generation study in rats and in developmental toxicity studies in rats and rabbits. The substance did not result in specific effects on reproduction or development. It is proposed that napropamide-M should not be classified for reproductive toxicity.
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.	n/a	n/a	Not applicable as napropamide-M is not considered to be a a reproductive toxicant.
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE classified or**		X	Not applicable – the active substance is proposed not to be classified for either

	proposed for classification in accordance with the provisions of Regulation (EC) No 1272/2008, as **carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties**			carcinogenicity or reproductive toxicity.
ii)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **toxic for reproduction category 2 and** in addition the RMS considers the substance **has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties**		X	Not applicable – the active substance is proposed not to be classified for reproductive toxicity and did not exhibit toxic effects on the endocrine organs.
iii)	Linked to either i) or ii) immediately above. 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.	n/a	n/a	Not applicable
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.		X	

Criterion	Napropamide-M Data	Criteria met?
Persistence DT50 (water) > 2 months DT50 (soil) > 6 months DT50 (sediment) > 6 months	DT50 (water) 5.53 d (water sediment study) DT50 (water) >1000 d (aerobic surface water study) DT50 (sediment) 333 d (water sediment study) DT50 (soil) (101 d (field dissipation study)	Yes
Bioaccumulation BCF or BAF > 5000 or in absence log K_{OW} > 5 or evidence that the substance, presents other reasons for concern, such as high bioaccumulation in other non-target species, high toxicity or ecotoxicity.	BCF (aquatics) 98 (Lepomis macrochirus)	No

				Potential for long-range transport Monitoring data showing that long range transport (LRT) may have occurred via air, water or migrating species or fate properties or modelling demonstrating LRT or DT50 (air) > 2 days for a chemical migrating through the air	DT50 (air) 0.046 d	No
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.		X	Criterion Persistence — the half-life in marine water is higher than 60 days, — the half-life in fresh or estuarine water is higher than 40 days, — the half-life in marine sediment is higher than 180 days, — the half-life in fresh or estuarine water sediment is higher than 120 days, or — the half-life in soil is higher than 120 days. Assessment of persistency in the environment shall be based on available half-life data collected under appropriate conditions, which shall be described by the applicant.	Napropamide-M Data DT50 (water) 5.53 d (water sediment study) DT50 (water) >1000 d (aerobic surface water study) DT50 (sediment) 333 d (water sediment study) DT50 (soil) (101 d (field dissipation study)	Criteria met? Yes

				Bioaccumulation BCF > 2000, or in absence log K_{OW} > 5, or evidence that the substance, presents other reasons for concern, such as high bioaccumulation in other non-target species, high toxicity or ecotoxicity.	BCF (aquatics) 98 (Lepomis macrochirus)	No
				Toxicity - the long-term no-observed effect concentration for marine or freshwater organisms is < 0.01 mg/l, - substance is classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) pursuant to Regulation (EC) No 1272/2008, or - there is other evidence of chronic toxicity, as identified by the classifications STOT RE 1 or STOT RE 2 pursuant to Regulation (EC) No 1272/2008.	Long term NOEC (Daphnia magna) 0.3 Substance is not classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) pursuant to Regulation (EC) No 1272/2008,. The active substance is not classified as STOT RE 1 or STOT RE 2 pursuant to Regulation (EC) No 1272/2008.	No
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.		X	Criterion	Napropamide-M Data	Criteria met?
				Persistence — the half-life in marine, fresh- or estuarine water is higher than 60 days, — the half-life in marine, fresh- or estuarine water sediment is higher than 180 days, or	DT50 (water) 5.53 d (water sediment study) DT50 (water) >1000 d (aerobic surface water study) DT50 (sediment) 333 d (water sediment study) DT50 (soil) (101 d (field dissipation study)	Yes

				— the half-life in soil is higher than 180 days.		
				Bioaccumulation BCF > 5000	BCF (aquatics) 98 (Lepomis macrochirus)	No
Ecotoxicology						
		Yes	No			
	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 organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.	X		Acute and reproductive risks to birds and mammals are shown to be acceptable at screening step. The risk from seconday poisoning was also shown to be acceptable for napropamide-M and the relevan metabolites. The risk to aquatic macrophytes from the active substance is unresolved at FOCUS step 4 for the scenarios D2 ditch, D2 (Winter oliseed rape). Acceptable risks to bees and other non-target arthropods are demonstrated at first tier. Low risks to soil organisms are also demonstrated. Risk mitigation is required to resolve the risk to terrestrial non-target plants (e.g. 5 m buffer zone). A low risk to microorganisms in sewage was identified. The above applies to all representative use (see sections B.9.1 to B.9.14 of Volume 3 (PPP) for further details).		
	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance **HAS** endocrine disrupting properties that may cause adverse effects on non-target organisms.		X	Based on the mammalian toxicology assessment, napropamide-M is not considered an endocrine disrupter and does not meet the interim criteria for this currently established in Regulation 1107/2009 (i.e. it is not classified for carcogenicity and reprotoxicity and does not have toxic effects on endocrine organs). The applicant has proposed that the active substance does not have endocrine disrupting properties.		
	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.	X		Napropamide-M is not considered an endocrine disrupter.		
	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	X		The risk assessment for honey bees (*Apis melifera*) indicated an acceptable risk based on first tier assessment (see Volume 1, Section 2.9.3.1 for the risk assessment summary). The risk was acceptable for all the representative uses and products considered by the assessment. The risk assessment was conducted according to SANCO/10329/2002, the guidance available at the time of the assessment. Therefore, no formal consideration of effects on colony survival and development has been conducted, as this is not part of the SANCO/10329/2002 risk assessment procedure.		

	honeybee larvae and honeybee behaviour.			
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.	X		The following environmental residue definitions have been established: <u>Risk Assessment</u> Food of plant origin: napropamide (sum of the R- and S- isomers at any ratio) Food of animal origin: Not required residues intakes by livestock are <0.004 mg/kg bw/day Soil: napropamide-M Groundwater: napropamide-M Surface water: napropamide-M and metabolites isomer-I, isomer-II and 1-naphthol Sediment: napropamide-M Air: napropamide-M <u>Monitoring</u> Food of plant origin: napropamide (sum of the R- and S- isomers at any ratio) Food of animal origin: Not required residues intakes by livestock are <0.004 mg/kg bw/day See level 2 (2.13) for detailed assessment
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 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.	X		Calculations for estimating PEC_{GW} of napropamide-M were performed using the models PEARL, PELMO and MACRO. Simulations were run for both representative GAP crop types, winter oilseed rape and brassicas. Annual average 80^{th} percentile PEC_{GW} concentrations at 1m depth were at least three orders of magnitude below the regulatory threshold of 0.1 µg/l for both crop types, across all three models. The RMS concludes that the groundwater leaching risk for napropamide-M is negligible. No major metabolites were observed in any of the soil laboratory or field dissipation studies to be considered in the groundwater exposure assessment.

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	It is considered as a result of this evaluation that Napropamide-M **does not meet the criteria** necessary to identify it as a candidate for substitution.

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.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.		X	Napropamide-M is not regarded as low risk because of the proposed environmental classification: **Acute Category 1** "H410 very toxic to aquatic life" based on the lowest acute toxicity endpoint for the active substance is an ErC_{50} of 0.0749 mg a.s./L for toxicity to aquatic macrophytes (fish LC_{50} 11.2 mg a.s./L, aquatic invertebrate EC_{50} 19 mg a.s./L and algae ErC_{50} of 28.8 mg/L). As this is <1 mg/L, acute category 1 applies to the active substance **Chronic Category 1** "H410 very toxic to aquatic life with long lasting effects" based on the lowest chronic toxicity endpoint for the active substance is an NOEC (EC_{10} value taken as true NOEC could not be determined) of 0.003 mg a.s/L for toxicity to aquatic macrophytes (fish NOEC >0.4 mg a.s/L, aquatic invertebrate NOEC 0.3 mg a.s./L and algae NOEC 0.8 mg a.s./L). As this is <0.1 mg/L and the substance is not rapidly degradable, chronic category 1 applies to the active substance. Napropamide-M also has a half life in soil >60 days. Soil DT_{50}= 101 days (single worst case from field dissipation trials) and is therefore persistent

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**
3.1.4.1. Identity of the active substance or formulation				
No data gaps identified				
3.1.4.2. Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
No data gaps identified				
3.1.4.3. Data on uses and efficacy				
No data gaps identified				
3.1.4.4. Data on handling, storage, transport, packaging and labelling				
No data gaps identified				
3.1.4.5. Methods of analysis				
A full set of validation data (generated in accordance with the SANCO/3029/99 rev.4 guidance document) is required to support the methodology described within (Report No. D03526) - Pothmann, 2011	For all uses	X		
3.1.4.6. Toxicology and metabolism				
No data gaps identified.				

3.1.4.7. Residue data				
Residue trials conducted at the proposed GAP appropriate to support the use on kale, chinese cabbage and kohl rabi.	Appropriate only to the kale, chinese cabbage and kohl rabi uses.	X		
3.1.4.8. Environmental fate and behaviour				
No data gaps identified				
3.1.4.9. Ecotoxicology				
Algal toxicity study with the active substance	For all uses	X		
Chronic toxicity to bees	For all uses	X		
Effects on honeybee development and other honeybee life stages	For all uses	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)**
Due to insufficient residue trial data, the uses on kale, chinese cabbage and kohl rabi could not be supported.	Approporiate only to the kale, chinese cabbage and kohl rabi 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)**
The risk to aquatic macrophytes (unresolved at FOCUS step 4) in D2 ditch and D2 stream scenarios.	Relevant to the representative use in winter oliseed rape.

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		Winter oil seed rape	Brassicas
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 (Aquatic macrpohytes, FOCUS step 4 scenarios: D2 ditch, D2	-
	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	-	-
	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**
None identified	All representative uses

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
No Co-RMS has been assigned to this evaluation.		

3.2. PROPOSED DECISION

It is proposed that:

[redacted]

It is considered that the following is specified in Part A of the Commission Implementing Regulation for the approval of the active substance:

- [redacted]

It is considered that the following be specified in Part B of the Commission Implementing Regulation as areas requiring particular attention from Member States when evaluating applications for product authorisation(s):

- [redacted]
- [redacted]
- [redacted]

It is considered that it should be specified that conditions of use shall include risk mitigation measures, where appropriate.

It is proposed that the Member States concerned shall request the submission of confirmatory information:
(a) where new data requirements are established during the evaluation process, or
(b) as a result of new scientific and technical knowledge, or
(c) to increase confidence in the decision.

- [redacted]

3.3. RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPORVAL OR AUTHORISATION(S), AS APPROPRIATE

3.3.1. Particular conditions proposed to be taken into account to manage the risks identified

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

3.4. APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

General:

- Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under council directive 91/414/EEC Sanco/221/2000 rev.10
- 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 4.0 November 2013

Volume 3 B5: Analytical Methods:

- SANCO/3030/99 rev.4: Technical Material and preparations: 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/3029/99 rev .4: Residues: 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/825/00 rev.8.1: Guidance document on pesticide residues analytical methods

Volume 3 B6: Mammalian toxicology:

- Guidance on Dermal Absorption, EFSA Journal 2012;10(4):2665
- Draft guidance on setting and application of acceptable operator exposure levels (AOELs) SANCO 7531 rev.10 (July 2006)
- Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009, SANCO/10597/2003-rev. 10.1 (July 2012)

Volume 3 B7: Residues:

- EC (European Commission), 1996. Appendix G. Livestock Feeding Studies. 7031/VI/95 rev.4.
- EC (European Commission), 1997a. Appendix A. Metabolism and distribution in plants. 7028/IV/95-rev.3.
- EC (European Commission), 1997b. Appendix B. General recommendations for the design, preparation and realization of residue trials. Annex 2. Classification of (minor) crops not listed in the Appendix of Council Directive 90/642/EEC. 7029/VI/95-rev.6.
- EC (European Commission), 1997c. Appendix C. Testing of plant protection products in rotational crops. 7524/VI/95-rev.2.
- EC (European Commission), 1997d. Appendix E. Processing studies. 7035/VI/95-rev.5.
- EC (European Commission), 1997e. Appendix F. Metabolism and distribution in domestic animals. 7030/VI/95-rev.3.
- EC (European Commission), 1997f. Appendix H. Storage stability of residue samples. 7032/VI/95-rev.5.

- EC (European Commission), 1997g. Appendix I. Calculation of maximum residue level and safety intervals. 7039/VI/95. As amended by the document: classes to be used for the setting of EU pesticide maximum residue levels (MRLs). SANCO 10634/2010.
- EC (European Commission), 2010. Classes to be used for the setting of EU pesticide Maximum Residue Levels (MRLs). SANCO 10634/2010 Rev. 0, finalized in the Standing Committee on the Food Chain and Animal Health at its meeting of 23-24 March 2010.
- EC (European Commission), 2011. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. 7525/VI/95-rev.9.
- FAO (Food and Agriculture Organization of the United Nations), 2009. Submission and evaluation of pesticide residues data for the estimation of Maximum Residue Levels in food and feed. Pesticide Residues. 2nd Ed. FAO Plant Production and Protection Paper 197, 264 pp.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in crops. No. 501, OECD, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in rotational crops. No 502, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in livestock, No. 503, OECD, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Residues in rotational crops (limited field studies). No 504, Paris 2007.
- OECD, 2007. OECD Guidelines for the testing of chemicals – Stability of pesticide residues in stored commodities. No 506, OECD, Paris 2007.
- OECD, 2007. OECD Guidelines for the testing of chemicals – Nature of the pesticide residues in processed commodities, high temperature hydrolysis. No 507, Paris 2007.
- OECD, 2008. OECD Guidelines for the testing of chemicals – Magnitude of pesticide residues in processed commodities. No 508, Paris 2008.
- OECD, 2009. OECD Guidelines for the testing of chemicals – Crop field trial. No 509, Paris 2009.

Volume 3 B8: Environmental Fate and Behaviour:

- Guidance document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU registration; SANCO/10058/2005, version 2.0, June 2006.
- FOCUS groundwater scenarios in the EU review of active substances; SANCO/321/2000 rev. 2.
- Generic guidance for Tier 1 FOCUS groundwater assessments; Version 2.0, January 2011.
- FOCUS surface water scenarios in the EU evaluation process under 91/414/EEC. SANCO/4802/2001-rev.2 final, May 2003.
- Generic guidance for FOCUS surface water scenarios; Version 1.1, March 2012.
- 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.

Volume 3 B9: Ecotoxicology:

- European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals, EFSA Journal 2009; 7(12):1438.
- European Food Safety Authority; Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290
- Guidance Document on Aquatic Ecotoxicology in the context of Directive 91/414/EEC, SANCO/3268/2001 rev 4 (final) 17 October 2002;
- Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC, SANCO/10329/2002, rev 2 (final) 17 October 2002;
- Candolfi et al. (2001). Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. ESCORT 2 workshop (European Standard Characteristics of Non-Target Arthropod Regulatory Testing), Wageningen, NL, 21-23 March 2000, SETAC Europe. SETAC publication, August 2001

3.5. REFERENCE LIST

Denmark, 2005. Draft Assessment Report (DAR) on the active substance napropamide prepared by the rapporteur Member State Denmark in the framework of Directive 91/414/EEC, September 2005

Denmark, 2008. Final Addendum to Draft Assessment Report on napropamide, compiled by EFSA, January 2008.

Denmark, 2009. Additional Report to the Draft Assessment Report (DAR) on the active substance napropamide prepared by the rapporteur Member State Denmark in the framework of Commission Regulation (EC) No 33/2008, June 2009.

Denmark 2010, Final Addendum to the Additional Report on napropamide, compiled by EFSA, January 2010.

European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance napropamide. EFSA Journal 2010; 8(4): 1565