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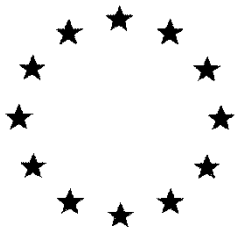

Draft Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009

Napropamide-M

Volume 3 – B.6 (PPP) – D-Devrinol

Rapporteur Member State: United Kingdom

Version History

When	What
June 2017	Initial DAR

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B.6. TOXICOLOGY AND METABOLISM DATA AND ASSESSMENT OF RISKS FOR HUMANS

Methods of analysis

The methods submitted for the active substance are applicable in most cases and these methods were fully validated in accordance with SANCO3030/99/rev.4 (see Section B.5). A method for the determination of active substance content from napropamide-M 450 g/L SC formulation (Report No. J19546, [redacted], 2011) has also been provided. This method has not been validated in accordance with SANCO/3030/99 rev.4 (see Volume 3 CP Section B.5) however this is not considered to undermine the validity of the study.

B.6.1. ACUTE TOXICITY OF PLANT PROTECTION PRODUCT

Acute toxicity studies were conducted on the representative napropamide-M formulation (D-Devrinol 450 SC, product code HBW03), which is a suspension concentrate containing napropamide-M (technical material) at a concentration of 466.3 g/L (42.8 % w/w).

Summary of acute toxicity, primary irritation and sensitisation studies

Type of study	Species	Result	Reference
Acute oral toxicity	Rat	LD_{50} >2000 mg/kg bw	[redacted] 2010a (Report No.: D03504)
Acute dermal toxicity	Rat	LD_{50} >2000 mg/kg bw	[redacted], 2010b (Report No.: D03515)
Acute inhalation toxicity	Rat	LC_{50} >3.3 mg/L	[redacted], 2011 (Report No.: D03526)
Skin irritation	Rabbit	Non-irritant	[redacted], 2010c (Report No.: D03537)
Eye irritation	Rabbit	Non-irritant	[redacted], 2011 (Report No.: D03548)
Skin sensitisation (LLNA)	Mouse	Non -sensitizer	[redacted], 2011 (Report No.: 1365301)

Based on the results of these studies it is concluded that D-Devrinol 450 SC is of low acute toxicity by the oral, dermal and inhalation routes of administration.

It does not meet the requirements for classification as irritant to the skin or eyes and it is considered not to be a skin sensitiser.

The *in vivo* studies on skin and eye irritation were commissioned before June 14th 2011 and have therefore been accepted.

According to the CLP Regulation (EC) No. 1272/2008, the formulation does not require classification.

B.6.1.1. Oral

The acute-toxic-class method has been used to investigate the acute oral toxicity of D-Devrinol 450 SC.

Table B.6.1.1. Summary of the acute oral toxicity of D-Devrinol 450 SC

Method Guideline, GLP status, reference	Species, strain, sex, no./group	Test substance, dose levels, duration of exposure	LD50	Remarks
OECD 423 (2001) (acute toxic class method) GLP Report CP 7.1.1/1 (No.: D03504) [redacted], 2010a	Rats / Wistar / 3 females / group Observation period: 14 days	2000 mg/kg bw suspended in purified water Formulation code : HBW03 Batch : JM230	> 2000 mg/kg bw	No deaths. No abnormal clinical signs. No adverse macroscopic findings at necropsy.

In an acute oral toxicity study performed in accordance with the acute toxic class method (OECD 423), 2000 mg/kg bw D-Devrinol 450 SC was administered to three fasted female rats. As no deaths occurred in this group, the result was confirmed in three additional animals at the same dose level.

None of the animals died and no abnormal clinical observations were recorded. The mean body weight of the animals declined slightly over the study period (within the normal range).

On the basis of this study, it is concluded that D-Devrinol 450 SC is not acutely toxic by the oral route (LD50 > 2000 mg/kg bw) and does not meet the criteria for classification.

B.6.1.2. Dermal

One acute dermal toxicity study is available, which was conducted in rats.

Table B.6.1.2. Summary of the acute dermal toxicity of D-Devrinol 450 SC

Method Guideline, GLP status, reference	Species, strain, sex, no./group	Test substance, dose levels, duration of exposure	LD50	Remarks
OECD 402 (1987) GLP Report CP 7.1.2/1 No.: D03515) [redacted], 2010b	Rat, Wistar, 5/sex Observation period: 14 days	2000 mg/kg bw suspended in purified water, applied for 24 hours Formulation code: HBW03 Batch : JM230	> 2000 mg/kg bw	No deaths. No signs of systemic toxicity. Slight skin effects (from test day 2 (after removal of the dressing) to test day 4. No adverse macroscopic necropsy findings.

In an acute dermal toxicity study, rats were exposed to a single limit dose of 2000 mg/kg bw for 24 hours under a semi-occlusive dressing. The application area comprised approximately 10% of the total body surface area. At the end of the 24-hour exposure period, the dressing was removed and the application site was flushed with lukewarm water. Skin effects were monitored 30 minutes to 5 hours after removal of the dressing, daily thereafter.

There were no deaths, signs of systemic toxicity or adverse macroscopic findings at necropsy. Very slight erythema was observed in all animals from test day 2 (after removing the dressing) to test day 4.

The mean body weights of the animals was within the normal range throughout the study period.

On the basis of this study, it is concluded that D-Devrinol 450 SC is not acutely toxic by the dermal route (LD50 > 2000 mg/kg bw) and does not meet the criteria for classification.

B.6.1.3. Inhalation

A limit test to investigate the acute toxicity of D-Devrinol 450 SC by the inhalation route has been conducted in rats.

Table B.6.1.3. Summary of studies to investigate the acute inhalation toxicity of D-Devrinol 450 SC

Method Guideline, GLP status, reference	**Species, strain, sex, no./group**	**Test substance, dose levels, duration of exposure**	**LC50**	**Remarks**
Acute inhalation toxicity OECD 403 (2009) GLP Report CP 7.1.3/1 (No.: D03526) [redacted], 2011	Rat, Wistar, 5/sex Nose only exposure Observation period: 14 days	3.3 mg/l (chemically determined concentration) as a liquid aerosol for 4 hours Formulation code: HBW03 Batch : JM230 Mass median aerodynamic diameters (MMADs) of 3.80 µm to 4.72 µm.	> 3.3 mg/l	No deaths. Clinical signs : none from test day 2 onwards. Salivation (all animals during exposure and immediately after exposure), mydriasis and ruffled fur (all animals immediately and two hours after exposure). No adverse macroscopic necropsy findings.

In an acute inhalation study, rats were exposed in a nose-only system for four hours to a limit concentration of 3.3 mg/l of D-Devrinol 450 SC as a liquid aerosol. There were no deaths. General indications of toxicity and respiratory effects that are commonly associated with the inhalation route of exposure were observed between exposure and 2 days after the exposure. No clinical symptoms were recorded from day 2 onwards. Body weights increased as expected from day 2 onwards, and there were no adverse macroscopic findings upon necropsy.

The MMADs of 3.80 µm to 4.72 µm were above the target range (1 to 4 µm). Geometric Standard Deviations (GSD) were also slightly above the target range (1.5 to 3). Nevertheless, the particle size distributions obtained are considered to be respirable to rats, appropriate for acute inhalation toxicity testing (44 - 52 % of particles were below 4 µm) and are not considered to invalidate the study.

The samples were analyzed using an HPLC method that has not been fully validated, however, this is not thought to invalidate the study.

On the basis of this study, it is concluded that D-Devrinol 450 SC is not acutely toxic by the inhalation route (LC50 > 3.3 mg/l) and thus does not meet the criteria for classification.

B.6.1.4. Skin irritation

Information on the skin irritation potential of D-Devrinol 450 SC is available from a GLP-compliant rabbit study.

Table B.6.1.4. Summary of the skin irritation studies with D-Devrinol 450 SC

Method Guideline, GLP status, reference	Test system	Test substance, dose levels, duration of exposure	Results
Primary Skin Irritation Rabbits OECD 404 GLP Report CP 7.1.4/1 (No.: D03537) [redacted], 2010c	Adult New Zealand White rabbits, 3 males.	0.5 ml of test item applied to intact skin for 4 hours. Formulation code: HBW03 Batch Number: JM230	The individual mean erythema/eschar score of the three animals was 1.00, 0.00 and 0.00, respectively and the individual mean oedema score was 0.00 for all three animals.

An *in vivo* study of the skin irritation potential of D-Devrinol 450 SC was investigated according to OECD test guideline No. 404. The test item was applied by topical semi-occulsive application of 0.5 ml to the intact skin of the left flank of each of three young adult New Zealand White rabbits. The duration of treatment was four hours. The scoring of skin reactions was performed at 1, 24, 48 and 72 hours, as well as 7 days after removal of the dressing.

The mean score was calculated separately for each animal at 3 scoring times (24, 48 and 72 hours after patch removal) for both erythema/ eschar and oedema grading. The individual mean erythema/eschar score of the three animals was 1.00, 0.00 and 0.00 and the individual mean oedema score was 0.00 for all three animals.

The application of the test item to the skin resulted in very slight erythema 1 hour post removal of the dressing in two of the three animals. This erythema persisted in one animal up until the 72 hour reading. Any effects seen were reversible and were no longer present 7 days after treatment. There was no staining of the skin with the test item. There were no corrosive effects noted on the treated skin of any animal at any of the intervals nor were there any clinical signs observed. The test item did not induce significant or irreversible damage to the skin.

According to Regulation (EC) 1272/2008 D-Devrinol 450 SC does not meet the criteria for classification as a skin irritant, under the conditions of this study.

B.6.1.5. Eye irritation

An *in vivo* eye irritation study in rabbits was undertaken to assess the eye irritation potential of D-Devrinol 450 SC.

Table B.6.1.5. Summary of the eye irritation studies with D-Devrinol 450 SC

Method Guideline, GLP status, reference	Test system	Test substance, dose levels, duration of exposure	Results
Primary Eye Irritation OECD 405 GLP Report CP 7.1.5/1 (No.: D03548) [redacted], 2011	Adult New Zealand White rabbits, 3 males.	0.1 mL into the left eye of each animal Formulation code: HBW03 Batch Number: JM230	The individual mean scores for corneal opacity, iris light reflex, conjunctival chemosis, as well as conjunctival redness were 0.00 for all three animals.

The eye irritation potential of D-Devrinol 450 SC was investigated in rabbits in accordance with OECD test guideline No. 405. The test item was applied by instillation of 0.1 g into the left eye of each of three young adult New Zealand White rabbits. Recording and scoring of eye irritation effects was performed at 1, 24 , 48 and 72 hours after test item instillation.

The mean score was calculated separately for each animal at three scoring times: 24, 48 and 72 hours folowing test item instillation. Irritation measurements recorded were: corneal opacity, iris light reflex, redness and chemosis of the conjunctivae. The individual mean scores for corneal opacity, iris light reflex, conjunctival chemosis, as well as conjunctival redness were 0.00 for all three animals.

The instillation of D-Devrinol 450 SC into the eye resulted in mild, early-onset and transient ocular changes, such as reddening of the conjunctivae and sclerae. All observed effects were reversible and were no longer evident 24 hours after test item instillation. There were no abnormal observations in the cornea or for the iris light reflex in any animals at any examination. There was no corrosion observed at any measurement interval nor staining of the treated eyes by the test item. There were no noted clinical signs.

According to Regulation (EC) 1272/2008 D-Devrinol 450 SC does not meet the criteria for classification as an eye irritant, under the conditions of this study.

B.6.1.6. Skin sensitization

Table B.6.1.6. Summary of the skin sensitisation studies with D-Devrinol 450 SC

Method, Guideline, GLP status, reference	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results
Local lymph node assay (LLNA) in mice OECD 429 GLP Report CP 7.1.6/1 (No.: 1365301) [redacted], 2011	Mice, CBA/CaOlaHsd 5 females per group. 2 animals in pre test. Total animals: 32	Test item concentrations of 20, 50, and 100 % (w/w). Test item vehicle: dimethylformamide Formulation code: HBW03 Batch No.: JM230	In this study Stimulation Indices (S.I.) of 1.53, 1.62, and 1.56 were determined with the test item at concentrations of 20, 50, and 100 % in dimethylformamide, respectively. The S.I. determined with the concurrent positive control (alpha-hexylcinnamaldehyde, tech. 25% in acetone:olive oil 4+1 v/v) was 10.03.

In this study the test item D-Devrinol 450 SC was assessed for its possible contact allergenic potential.

To determine the highest non-irritant test item concentration that does not induce signs of systemic toxicity, a pre-test was performed in two animals. Two mice were treated with the test item by epidermal topical application to the dorsal surface of each ear at concentrations of 50 and 100 % once daily each on three consecutive days. Prior to the first application of the test item and before sacrifice the body weight of the animals was determined. Clinical signs were also recorded daily.

Skin irritation was considered to be excessive if reddening of the skin of the ear of a score value of 3 was observed at any observation time and/or if an increase in ear thickness of ≥25 % was recorded on day 3 or day 6.

Signs of systemic toxicity were not observed during the pre-test. The animals treated with undiluted test item showed reddening of the ear skin (Score 1) on day 5 of the pre-test. Animals treated with a 50 % solution of the test item did not show any signs of local skin irritation.

The test item in the main study was assayed at 20, 50, and 100 % (w/w). The animals did not show any clinical signs during the course of the study and no cases of mortality were observed. In this study, stimulation indices (S.I) of 1.53, 1.62 and 1.56 were determined with the test item at concentrations of 20, 50 and 100 % in dimethylformamide, respectively. The S.I determined with the positive control was 10.03, demonstrating the validity of this study.

The test item D-Devrinol 450 SC was not a skin sensitiser under the conditions of this study and does not meet the criteria for classification.

B.6.1.7. Supplementary studies on the plant protection product

There are no supplementary studies on the plant protection product.

B.6.1.8. Supplementary studies for combinations of plant protection products

There are no supplementary studies combinations of plant protection products.

B.6.2. DERMAL ABSORPTION

B.6.2.1. In vitro dermal absorption study with Napropamide-M 450 SC

Study	Napropamide-M 450 g/L blank formulation (SC) *In Vitro* Dermal Absorption Study Using Human Skin.
Reference	I.R. Johnson (2014)
Date performed (experimental phase)	27 August 2013 to 6 November 2013
Test facility	Dermal Technology Laboratory Ltd. Med IC4 Keele University Science and Business Park Keele, Staffordshire, ST5 5NL, UK
Report reference	Report number JV2242-REG
Guidelines	OECD Guideline for the testing of chemicals. Guideline 428 skin absorption : i*n vitro* method (2004) OECD Environmental health and safety publication series on testing and assessment no. 28. Guidance document for the conduct of skin absorption studies (2004)

Deviations from the guideline	None
GLP	Yes
Test material	[^{14}C]-napropamide-M (radiochemical purity >99%, chiral purity >99.9% (no undesired isomer observed), specific activity 7.6 MBq/mg) applied as: • a 450 g a.s./L SC formulation of 'Napropamide-M 450 g/L blank formulation' • a 1.3 g a.s./L aqueous dilution of 'Napropamide-M 450 g/L blank formulation'
Study acceptable	Yes

Method

The *in vitro* dermal absorption of [14C]-napropamide-M (radiochemical purity > 99%) was investigated in human skin using a 450 g/L SC formulation ('Napropamide-M 450 g/L blank formulation'1) and an aqueous dilution of the formulation containing 1.3 g a.s./L. The concentration of the tested dilution is just slightly higher than the most dilute in-use solution (1.275 g napropamide-M / L of spray solution, according to Document D-1 (Intended uses supported in the EU for which data have been provided, dated June 2015). Therefore, the tested solution is representative of the proposed use.

Human skin samples from 7 donors (all female, aged between 37 and 88, skin taken from back or abdomen) were obtained from a tissue bank and stored at < -20 °C on aluminium foil for between 63 and 123 days before use. Skin sections were cut at a thickness setting of 400 µm using an electric dermatome; no other details were provided regarding the processing of the samples.

Skin samples were mounted (stratum corneum uppermost) in static glass diffusion cells with an exposed membrane area of 2.54 cm^2 in each cell. The high dose and low dose test groups each used 8 cells with skin from 4 and 5 different donors, respectively. The diffusion cells were maintained at 32 °C ± 1 °C.

Before the start of the experiment, skin integrity was determined by measurement of the electrical resistance across the sample. Skin samples with a measured resistance of <10 kΩ were regarded as having a lower integrity than normal and not used for exposure to the test materials. The receptor fluid of 50% v/v ethanol in water was stirred continuously while in the receptor chamber. The solubility of napropamide-M in the receptor fluid was determined experimentally and shown to be unlikely to limit the rate of dermal absorption in the study.

The nominal dose levels were achieved by applying the test materials at a rate of 10 µl/cm^2 to the exposed skin surface area within the donor chamber. The applications were left unoccluded for the duration of the experiment (24 hours). After an exposure period of 6 hours (i.e. after the 6 hours sample had been taken), the test compound was removed from the application site using natural sponge swabs pre-wetted with 3 % Teepol® L in water until no further radioactivity was removed (confirmed with a Geiger counter). Samples of the receptor fluid were taken at a series of time points over 24 hours using an autosampler.

Table B.6.2.1-1 Experimental details

Group	**Group size**	**Test material**	**Dose a.s. (µg/cm^2)* (applied as 10 µl of test material/cm^2)**	**Receptor fluid sampling (hours after application)**
Concentrate	8	SC formulation 450 g a.s./L Achieved concentration : 411 g/kg (448 g/L)	Nominal dose 4000 µg a.s./cm^2 Mean actual dose 4107 µg a.s./cm^2	1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours

[1] The blank formulation contained all the ingredients of the commercial formulation concentrate with the exception of the active ingredient, napropamide-M.

Dilution	8	Aqueous dilution 1.3 g a.s./L Achieved concentration : 1.33 g/kg (1.33 g/L)	Nominal dose 13.3 µg a.s./cm^2 Mean actual dose 13.3 µg a.s./cm^2	1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours

Footnote:
*: The radioactivity content of each formulated [^{14}C]-Napropamide-M preparation was determined by analysing sub-samples of solvent dilutions by LSC.

At the end of the study (after the 24 hour sample had been taken) the skin samples were swabbed again (as described above and, additionally, with further sponges pre-wetted with water) to remove surface residues. Radioactivity was determined by liquid scintillation counting (LSC using a Packard 3100 TR) in the receptor fluid samples, skin wash swabs (solubilised in Soluene® 350) and donor chamber (washed with ethanol).

Tape stripping of the skin using adhesive tape (Scotch 3M Magic Tape) was carried out to remove the residual dose and the stratum corneum, to a maximum of 5 strips. Each tape strip was individually solubilised in ethanol and analysed by LSC. The remaining skin was carefully removed from the receptor chamber, digested and analysed by LSC. After the final receptor fluid sample had been taken, the remaining receptor fluid in the system was retained and analysed. The conditions of storage of samples not analysed immediately is not mentioned however it is stated that stability data were generated that confirmed that formulated napropamide-M remains radiochemically stable for a period of time equivalent to that used in the study (24h). The LOQ for each of the matrices was calculated on the basis of the background (or pre-sample in the case of receptor fluid) cpm/dpm values.

In one case (Cell 34) it was not possible to take the full 5 strips as the epidermis began to tear. Therefore tape stripping was discontinued and the last tape strip for these cells was digested with the remaining skin so as not to underestimate residues in the remaining skin compartment. The remaining skin was carefully removed from the receptor chamber, digested and analysed by LSC.

Results and Discussion:

The solubility of the test article in the receptor fluid and the skin integrity were acceptable.

The distribution of napropamide-M was reported for the concentrate and in use dilution.

For the concentrate the absorbed fraction was calculated from the skin, tape strips, receptor fluid and receptor chamber wash.
For the in use dilution the absorbed fraction was calculated from the skin, receptor fluid and receptor chamber wash. The tape strips were excluded on the basis that more than 75 % of napropamide-M absorption from the dilution occurred in the first half of the experimental time (first 12 hours). Absorption data at each of the sampling points were not presented in tabular form; however the results were presented in graphical form and this was sufficient to verify that >75 % of napropamide-M absorption occurred in the first half of the experimental time.

For the concentrate, the percentage absorption is **0.6 %** based on the mean absorbed fraction (0.34 %) and the addition of the one standard deviation (0.25) as the standard deviation is greater than 25 % of the mean of the total absorption.

For the in-use dilution, the percentage absorption is **18 %** based on the absorbed fraction (14.06%) and the addition of one standard deviation (4.36) as the standard deviation is greater than 25% of the mean total absorption.

Table 6.2.1-2 Distribution and percentage absorption of Napropamide-M 450 g/L blank formulation concentrate (450g/L)

Units: %		cell:	1	fn	2	fn	3	fn	4	fn	5	fn	6	fn	7	fn	8	fn	
		cell ref:	1		3		5		8		26		30		32		34		**Mean (±SD)**
a	Receptor fluid		0.129		0.184		0.054		0.262		0.144		0.221		0.145		0.553		0.21 (± 0.15)
b	Receptor chamber			-		-		-		-		-		-		-		-	
c	Donor chamber		0.065		0.184		0.083		0.071		0.047		0.181		0.217		0.072		0.12 (± 0.07)
d	**Tape strips**																		
d1	1		0.002	*	0.004		0.002	*	0.023		0.001	*	0.003	*	0.004		0.014		0.007 (± 0.008)
d2	2		0.001	*	0.002	*	0.002	*	0.009		0.002	*	0.003	*	0.002	*	0.011		0.004 (± 0.004)
d3	3		0.001	*	0.001	*	0.002	*	0.014		0.001	*	0.027		0.008			×	0.008 (± 0.01)
d4	4		0.002	*	0.001	*	0.016		0.009		0.005		0.002	*	0.002	*		×	0.005 (± 0.005)
d5	5		0.000	*	0.003	*	0.001	*	0.009		0.0002	*	0.005		0.002	*		×	0.003 (± 0.003)
dd1	sub-total (1-5)		0.006		0.011		0.023		0.064		0.009		0.040		0.018		0.025		0.02 (± 0.02)
dd2	sub-total (3-5)		0.003		0.005		0.019		0.032		0.006		0.034		0.012		0.000		0.01 (± 0.01)
e1	Skin wash (6)		106.0		98.1		105.0		102.0		104.0		101.0		111.0		103.0		103.76 (± 3.82)
e2	Skin wash (24h)		0.193		1.030		1.190		1.450		0.320		1.090		2.000		1.050		1.04 (± 0.58)
f	Remaining skin[1]		0.036		0.052		0.033		0.349		0.072		0.066		0.069		0.248		0.12 (± 0.12)
g	**Total recovery**		**106.4**		**99.6**		**105.8**		**103.8**		**104.2**		**102.3**		**113.3**		**104.8**		105.03 (± 3.98)
h	**Total absorption[2]**		0.17		0.24		0.11		0.64		0.22		0.32		0.23		0.80		0.34 (± 0.25)
															mean + one standard deviation =				0.6

Footnotes (fn)

[1]: skin tissue remaining after tape stripping

[2]: a (receptor fluid) + b (receptor chamber) + dd2 (tape strips 3 to 5) + f (remaining skin)

*: <LOQ (Appendix 9) included in the calculation of the mean

×: tape strip not taken

-: no value

Table 6.2.1-3 Distribution and percentage absorption of Napropamide-M 450 g/L blank formulation in-use dilution (1.3 g/L)

Units: %		cell:	**1**	**fn**	**2**	**fn**	**3**	**fn**	**4**	**fn**	**5**	**fn**	**6**	**fn**	**7**	**fn**	**8**	**fn**	
		cell ref:	2		7		9		15		27		31		33		35		**Mean (±SD)**
a	Receptor fluid		8.45		10.10		9.98		10.80		13.40		13.40		11.70		19.30		12.14 (± 3.36)
b	Receptor chamber			-		-		-		-		-		-		-		-	
c	Donor chamber		0.033		0.073		0.392		0.047		0.183		0.300		0.095		0.157		0.16 (± 0.13)
d	**Stratum corneum**		0.053		0.081		0.111		0.076		0.091		0.061		0.073		0.072		0.08 (± 0.02)
e1	Skin wash (6h)		89.5		91.7		88.4		93.8		83.4		92.9		88.5		78.9		88.39 (± 5.03)
e2	Skin wash (24h)		1.21		2.41		3.79		1.43		5.64		2.39		1.71		2.24		2.6 (± 1.46)
f	Remaining skin[1]		0.613		1.050		2.090		0.460		6.850		0.899		1.090		1.670		1.84 (± 2.09)
g	**Total recovery**		**99.9**		**105.4**		**104.8**		**106.6**		**109.6**		**110.0**		**103.2**		**102.3**		105.21 (± 3.48)
h	**Total absorption[2]**		9.06		11.15		12.07		11.26		20.25		14.30		12.79		20.97		13.98 (± 4.36)
															mean + one standard deviation =				18

Footnotes (fn)

[1]: skin tissue remaining after tape stripping

[2]: a (receptor fluid) + b (receptor chamber) + f (remaining skin)

*: <LOQ (Appendix 9) included in the calculation of the mean

×: tape strip not taken

-: no value

Conclusion:

When the results of this study are interpreted in conjunction with the EFSA guidance on dermal absorption (2012) human dermal absorption values of 0.6 % and 18 % are obtained for napropamide-M in the concentrate (Napropamide-M 450, SC) and spray dilution (1.3 g napropamide-M per litre), respectively.

B.6.3. AVAILABLE TOXICOLOGICAL DATA RELATING TO CO-FORMULANTS

D-Devrinol 450 SC (product code HBW03)

The additonal labelling phrase EUH 208 is triggered by the presence of BIT (1,2-benzisothiazolin-3-one), present at a level ≥10 % of the SCL for BIT of 0.05 %.

No other classifcation of the product is triggered by the classification of the co-formulants, based on the information provided in the submitted SDS.

B.6.4. EXPOSURE DATA

B.6.4.1. Operator exposure

A summary of the application parameters pertinent to the operator, bystander, resident and worker exposure assessment for 'D-Devrinol 450-SC' are presented below.

Table B.6.4.1-1: Summary of 'D-Devrinol 450-SC' application parameters pertinent to the operator, bystander, resident and worker exposure assessment.

'D-Devrinol 450-SC'	
Formulation type	Suspension concentrate (SC), containing 450 g/L napropamide-M
Use	Pre-emergence herbicide to control annual grass and broad-leafed weeds in brassica vegetables and winter oil seed rape.
Application method	Tractor-mounted/trailed field crop sprayer
Max individual dose	1.7 L product/ha (0.765 kg a.s./ha)
Number of applications	1 per year
Application volume	200 to 600 L/ha
Max spray concentration	3.825 g a.s./L
Latest time of application	Pre-emergence (BBCH 08) for both brassica vegetables and winter oil seed rape
Packaging	1 L to 20 L containers
Classification	Not classified for human health effects
Systemic AOEL	0.5 mg/kg bw/day
Dermal absorption	0.6% for the concentrate, 18% for the spray dilution

Predicted levels of operator exposure to 'D-Devrinol 450-SC' have been calculated using UK POEM[2] and the German Model[3] and are presented below. Exposure estimate spreadsheets are in Appendix 1.

B.6.4.1.1 Estimate of Operator Exposure Using German Model

[2] Estimation of Exposure and Absorption of Pesticides by Spray Operators, Scientific subcommittee on Pesticides and British Agrochemical association Joint Medical Panel Report (UK MAFF), 1986 and the Predictive Operator Exposure Model (POEM) V 1.0, (UK MAFF), 1992, 2007 version. ("UK POEM").
[3] Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection), Mitteilungen aus der Biologischen Bundesanstalt für Land-und Forstwirtschaft, Berlin-Dahlem, Heft 277, 1992. ('German Model').

A standard bodyweight of 70 kg and a work rate of 20 ha/day is assumed. The results can be summarised as follows, with the full spreadsheets presented in Appendix 1 (Estimate 1).

Table B.6.4.1.1-1 German model estimate of exposure for operators applying 'D-Devrinol 450-SC': field crop sprayer

Dermal exposure mg/person/day		Inhalation exposure mg/person/day		Total systemic exposure*	
Mix/loading	Application	Mix/loading	Application	mg/kg bw/day	% of AOEL
No PPE					
36.7200	31.2120	0.0092	0.0153	0.0838	17
*Assuming dermal absorption values of 0.6% (concentrate) and 18% (spray dilution) AOEL 0.5 mg/kg bw/d					

Based on the German Model and using 'D-Devrinol 450-SC' as directed, the predicted level of operator exposure to napropamide-M is 17% of the systemic AOEL of 0.5 mg/kg bw/day without the use of PPE.

B.6.4.1.2 Estimate of Operator Exposure Using UK POEM

A standard bodyweight of 60 kg, a work rate of 50 ha/day and 10 litre container with 63mm is assumed. In the UK POEM model spray concentration does influence exposure such that the use of the lowest proposed water volume represents the worst case. The results can be summarised as follows, with full calculations presented in Appendix 1 (Estimate 2).

Table B.6.4.1.2-1 UK POEM estimate of exposure for operators applying 'D-Devrinol 450-SC': field crop sprayer

Dermal exposure mg/person/day		Inhalation exposure mg/person/day		Total systemic exposure*	
Mix/loading	Application	Mix/loading	Application	mg/kg bw/day	% of AOEL
No PPE					
202.5000	158.9288	Negligible	0.2295	0.5009	100
Gloves during mixing and loading					
10.1250	158.9288	Neligible	0.2295	0.4816	96
*Assuming dermal absorption values of 0.6% (concentrate) and 18% (spray dilution) AOEL 0.5 mg/kg bw/d					

Based on the UK POEM model and using 'D-Devrinol 450-SC' as directed, the predicted level of operator exposure to napropamide-M is equivalent to 100% of the systemic AOEL of 0.5 mg/kg without the use of PPE. The predicted level of operator exposure to napropamide-M is equivalent to 96% of the systemic AOEL with the use of gloves during mixing and loading. Given that exposure to napropamide-M is being driven by the application phase, the use of gloves during mixing and loading provides little additional protection.

B.6.4.2. Bystander and resident exposure

In the absence of a harmonised approach to bystander and resident exposure assessment throughout the EU, this evaluation presents calculations using both the UK (CRD) approach and the German (BfR) approach.

B.6.4.2.1 Bystander/Resident Exposure to Vapour (UK approach)

Exposure to vapour post application is not likely to be significant given the low vapour pressure of napropamide-M of 3.8 x 10^{-6} Pa at 25 °C and is not likely to present a concern. However, as a worse case, the level of bystander exposure to napropamide-M vapour following the use of 'D-Devrinol 450-SC' can be estimated using a surrogate value for residues in air adjacent to treated crops from Californian Environmental Protection Agency studies[4]. In these studies, a 24 ha orange orchard was treated with chlorpyrifos (vapour pressure 1.43 x 10^{-3} Pa at 20°C, 3.35 10^{-3} Pa at 25º C) using broadcast air-assisted sprayers. During application, wind speeds ranged from 2 to 20 km/h and the maximum temperature was 42 °C. Chlorpyrifos residues in air adjacent to the orchard were monitored over 72 hours. The highest 24 hour time-weighted average residue in air was 15 µg/m^3.

Bystander exposure to vapour can be calculated using these surrogate values and assuming:

- a body weight of 60 kg for an adult (based on the 50th percentile value for females aged 16 to 24 years in 1995-7 Health Surveys for England);
- a body weight of 15 kg for a small child (based on the average value for male and female children aged 2 and 3 years in 1995-7 Health Surveys for England);
- a respired volume of 15.2 m^3/day (based on mean values for the long term inhalation rate for adult males aged 19 to >65 years published in the United States Environmental Protection Agency (US EPA) Exposure Factors Handbook); and
- a respired volume of 8.3 m^3/day (based on mean values for the long term inhalation rate for children aged 3 to 5 years published in the US EPA Exposure Factors Handbook);

On this basis, potential exposure to vapour is estimated to be 0.0038 mg/kg bw/day for an adult and 0.0083 mg/kg bw/day for a child. These exposures are equivalent to <1% and 2% of the systemic AOEL of 0.5 mg/kg bw/day for napropamide-M for adults and children respectively.

B.6.4.2.2 Bystander/Resident Exposure to Spray Drift (UK approach)

Exposure through dermal and inhalation exposure to spray drift can be estimated on the basis of direct measurements of simulated bystander exposure for field crop sprayers in a UK study[5].

In this study, a single pass of the sprayer resulted in a mean potential dermal exposure (PDE) of 0.1 ml of spray solution on a bystander positioned 8 m downwind from the edge of the treatment area. Mean potential inhalation exposure (PIE) was 0.006 ml of spray solution.

Using these data, and assuming that there is no exposure reduction from clothing and there is 100% absorption and retention of potential inhalation exposure, total systemic exposure can be estimated as follows:

$$\text{Systemic Exposure} = \frac{(PDE \times SC \times DA) + (PIE \times SC)}{BW}$$

Where:
PDE = potential dermal exposure (0.1 ml spray)
PIE = potential inhalation exposure (0.006 ml spray)

[4] California Environmental Protection Agency, Air Resources Board (1998). Report for the application and ambient air monitoring for chlorpyrifos (and the oxon analogue) in Tulare County during spring/summer 1996.
[5] Lloyd, G.A. and Bell, G.J. 1983, Hydraulic nozzles: comparative spray drift study (MAFF/ADAS).

SC = concentration of active substance in spray (3.825 mg/ml)
DA = percentage dermal absorption (18% for the spray dilution)
BW = bodyweight (60 kg)

In this case:

$$\text{Systemic Exposure} = \frac{(0.1 \text{ ml} \times 3.825 \text{ mg/ml} \times 18\%) + (0.006 \times 3.825 \text{ mg/ml})}{60 \text{ kg}}$$

$$= 0.00153 \text{ mg/kg bw/day}$$

Estimated exposure is 0.00153 mg/kg bw/day equivalent to <1% of the systemic AOEL of 0.5 mg/kg bw/day. Comparing exposure arising from a single spray event to a chronic AOEL is protective of both bystanders (short term exposure) and residents (long term exposure). In the case of the latter, this reflects the unlikely scenario that exposure to spray drift occurs to the same extent each and every day throughout the season of use. The considerations of exposure to vapour and drift fallout apply to bystanders and residents for the same reason.

B.6.4.2.3 Bystander/Resident Exposure to Drift Fallout (UK approach)

The following calculations predict the amount of napropamide-M likely to be deposited in gardens next crops treated with 'D-Devrinol 450-SC' (due to fallout from spray drift) and the level of exposure likely to result when children playing in the garden are exposed through dermal, hand-to-mouth and object-to-mouth routes. These estimates are based on the spray drift fallout values for field crop sprayers used for the aquatic risk assessment[6] and US EPA values for residential exposure resulting from contact with treated lawns[7].

Spray drift fallout

Allowing for an untreated headland of 1 m, the level of fallout from spray drift at the boundary with a neighbouring area is predicted to be equivalent to 2.77% of the applied dose. This level of fallout deposit is predicted to decline to 0.57% at a distance of 5 m from the boundary. By integration, the average level of fallout over the whole area from the boundary to a point 3 m outside is estimated to be about 1%.

Children's dermal exposure

Systemic exposures via the dermal route are calculated using the above drift fallout values and the following equation:

[6] Rautmann, D., Streloke, M. and Winkler, R. (2001). New basic drift values in the authorisation procedure for plant protection products. In Forster, R. and Streloke, M. Workshop on risk assessment and risk mitigation measures in the context of the authorisation of plant protection products (WORMM). Mitt. Biol. Bundesanst. Land-Forstwirtsch. Berlin-Dahlem, Heft 381.

[7] USA EPA (1998). Occupational and residential exposure test guidelines: Group B, Post-application exposure monitoring test guidelines. Series 875 v 5.4.
USA EPA (2001). Recommended revisions to the standard operating procedures (SOPs) for residential exposure assessment. Science Advisory Council for Exposure Policy, 12.
USA EPA (1999). Overview of issues related to the standard operating procedures for residential exposure assessment. Presentation to the FIFRA Scientific Appraisal Panel.

$$SE_{(d)} = \frac{(AR \times DF \times TTR \times TC \times H \times DA)}{BW}$$

Where:
$SE_{(d)}$ = Systemic exposure via the dermal route.
AR = Total application rate, (one application at 1.7 L/ha product, 0.765 kg a.s/ha = 7.65 µg a.s./cm^2).
DF = Drift fallout value (assumed average of 1% from field crop (boom) sprayer applications).
TTR = Turf transferable residue (EPA default value is 5% derived from transferability studies with wet hands).
TC = Transfer coefficient (standard EPA value is 5200 cm^2/h).
H = Exposure duration for a typical day (assumed to be 2 hours which reflects the 75th percentile for toddlers playing on grass in the EPA Exposure Factors Handbook).
DA = Percent dermal absorption (18% for the spray dilution).
BW = Body weight (15 kg).

In this case:

$$SE_{(d)} = \frac{7.65\ \mu g\ a.s./cm^2 \times 1\% \times 5\% \times 5200\ cm^2/h \times 2h/d \times 18\%}{15\ kg\ bw}$$

$$= 0.4774\ \mu g/kg\ bw/day$$

Children's hand-to-mouth exposure

Hand-to-mouth exposures are calculated using turf transferable residue levels using the following equation:

$$SE_{(h)} = \frac{(AR \times DF \times TTR \times SE \times SA \times Freq \times H)}{BW}$$

Where:
$SE_{(h)}$ = Systemic exposure via the hand-to-mouth route.
AR = Total application rate, (one application at 1.7 L/ha product, 0.765 kg a.s/ha = 7.65 µg a.s./cm^2).
DF = Drift fallout value (assumed average of 1% from field crop (boom) sprayer applications).
TTR = Turf transferable residue (EPA default value is 5% derived from transferability studies with wet hands).
SE = Saliva extraction factor (default value is 50%).
SA = Surface area of the hands (20 cm^2, based on the assumption that this is the contact skin area each time a child puts a hand in his/ her mouth (this is equivalent to the palmar surface of three figures and is also related to the next parameter) .
Freq = Frequency of hand to mouth events/hour (20 events/hour for short term exposures - this is the 90th percentile of observations that ranges from 0 to 70 events/hour).
H = Exposure duration (2 hours).
BW = Body weight (15 kg).

In this case:

$$SE_{(h)} = \frac{7.65\ \mu g\ a.s./cm^2 \times 1\% \times 5\% \times 50\% \times 20\ cm^2 \times 20/h \times 2h/d}{15\ kg\ bw}$$

$$= 0.1020\ \mu g/kg\ bw/d$$

Children's object-to-mouth exposure

Object to mouth exposures were calculated using turf transferable residue levels and the following equation:

$$SE_{(o)} = \frac{(AR \times DF \times TTR \times IgR)}{BW}$$

Where

$SE_{(o)}$= Systemic exposure via mouthing activity.
AR = Total application rate (one application at 1.7 L/ha product, 0.765 kg a.s/ha = 7.65 µg a.s./cm^2).
DF = Drift fallout value (assumed average of 1% from field crop (boom) sprayer applications).
TTR = Turf transferable residues (default value of 20% for object to mouth assessments).
IgR = Ingestion rate for mouthing of grass (assumed to be equivalent to 25 cm^2 of grass/day).
BW = Body weight (15 kg)

In this case:

$$SE_{(o)} = \frac{7.65\ \mu g\ a.s./cm^2 \times 1\% \times 20\% \times 25\ cm^2}{15\ kg\ bw}$$

$$= 0.0255\ \mu g/kg\ bw/day$$

Children's total exposure

Children's total exposure was estimated as the sum of the dermal, hand-to-mouth, and object to mouth exposures.

$$SE_{(total)} = SE_{(d)} + SE_{(h)} + SE_{(o)}$$

$$= 0.097\ \mu g/kg\ bw/day$$

$$= 0.0006\ mg/kg\ bw/day$$

This equates to <1% of the AOEL for napropamide-M of 0.5 mg/kg bw/day.

B.6.4.2.4 Bystander/Resident Exposure to Spray Drift / Drift Fallout (German Approach)

The applicant has included bystander & resident exposure assessments conducted in accordance with the German (BfR) approach (Martin et al 2008 [8]). This is not used by the UK. No validation has been undertaken nor has any regulatory decision been made upon the assessments, however they have been left in this document for the information of other member states.

Bystander and resident exposure estimates using the German (BfR) approach are presented in Appendix 1 (Estimates 3 and 4) and are summarised in Table B.6.2.4-1.

In line with the BfR approach, these estimates are based on the following assumptions:

- Bystanders and residents will be lightly clothed adults (body weight 60 kg) and children (body weight 16.15 kg).
- Bystanders are located at the edge of the area being treated at a distance 10 m downwind from the sprayer and will be directly exposed to spray drift through dermal and inhalation routes.
- The spray equipment will take 5 minutes to pass the bystander.
- The level of spray drift reaching bystanders is 0.29% of the applied dose for field crop sprayers based on published deposition data.
- Bystander inhalation exposure will be no greater than that experienced by an unprotected sprayer operator, adjusted for the duration of exposure.
- Residential exposure will result from dermal contact with surfaces previously exposed to spray drift (2 hour exposure for adults and children in contact with a contaminated lawn), the inhalation of vapour (over 24 hours) and, for children aged between 2 years and 5 years, oral uptake by hand-to-mouth contact and by object-to-mouth contact.

Table B.6.4.2.4-1 Bystander and resident exposure to napropamide-M resulting from the use of 'D-Devrinol 450-SC' through field crop (boom) sprayers (BfR approach)

Group	Route-specific external exposure (mg/person/day)			Total systemic exposure *	
	Dermal	Inhalation	Oral	mg/kg bw/day**	% of AOEL
Bystander - Adult	0.00067	0.000004	not applicable	0.00067	<1
Bystander - Child	0.00052	0.000008	not applicable	0.00053	<1
Resident - Adult	0.000049	0.000276	not applicable	0.000325	<1
Resident - Child	0.000064	0.005146	0.000034	0.000613	<1
*	assuming a dermal absorption value of 18% for the spray dilution				
**	assuming a body weight of 60 kg for an adult and 16.15 kg for a child (default BfR values)				
AOEL	0.5 mg/kg bw/day				

The above estimates predict that the proposed uses of 'D-Devrinol 450-SC' will result in levels of systemic bystander and resident exposure to napropamide-M no greater than 0.00067 mg/kg bw/day. This is equivalent to <1% of the systemic AOEL of 0.5 mg/kg bw/day.

[8] Martin, S., Westphal, D., Erdtmann-Vourliotis, M., Dechet, F., Schulze-Rosario, C., Stauber, F., Wicke, H. and Chester, G. (2008). Guidance for exposure and risk evaluation for bystanders and residents exposed to plant protection products during and after application. J. Verbr. Lebensm. 3 (2008):272-281

B.6.4.3. Worker exposure

'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.

B.6.5. EXPOSURE AND RISK ASSESSMENT

Estimates based on surrogate data contained in the German Model predict that the proposed use of 'D-Devrinol 450-SC' through field crop sprayers will result in a level of systemic exposure to napropamide-M equivalent to 17% of the AOEL for an operator without the need for PPE. According to UK POEM operator exposure to napropamide-M is predicted to be 100% of the AOEL for an operator without the need for PPE.

On the basis these estimates and considering that the product is not classified for human health, the proposed use of 'D-Devrinol 450-SC' is considered to be acceptable without any operator protection requirements.

The UK approach predicts that the proposed use of 'D-Devrinol 450-SC' will result in the following levels of systemic exposure to napropamide-M for unprotected bystanders/residents:

- Vapour exposure to an adult = <1% of the AOEL
- Vapour exposure to a child = 2% of the AOEL
- Drift exposure = <1% of the AOEL
- Children's exposure to fallout = <1% of the AOEL

The German (BfR) approach predicts that the proposed use of 'D-Devrinol 450-SC' will result in the following levels of systemic exposure to napropamide-M for unprotected bystanders/residents:

- Exposure to adult bystander = <1% of the AOEL
- Exposure to child bystander = <1 % of the AOEL
- Exposure to adult resident = <1% of the AOEL
- Exposure to child resident = <1% of the AOEL

On the basis of these estimates, the level of exposure for unprotected bystanders and residents resulting from the proposed use of 'D-Devrinol 450-SC' is considered to be acceptable.

'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.

B.6.6. REFERENCES RELIED ON

Data Point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
CP 7.1.1/01	[redacted]	2010a	D-Devrinol 450 SC: acute oral toxicity study in rats Company Report No.: D03504 [redacted]. GLP, Unpublished	Y	Y	Data protection is claimed in accordance with Article 59 of Regulation (EC) No 1107/2009	D-Devrinol 450 SC: acute oral toxicity study in rats Company Report No.: D03504 Harlan Laboratories Ltd., Switzerland. GLP, Unpublished	None
CP 7.1.2/01	[redacted]	2010b	D-Devrinol 450 SC: acute dermal toxicity study in rats Company Report No.: D03515 [redacted] GLP, Unpublished	Y	Y	Data protection is claimed in accordance with Article 59 of Regulation (EC) No 1107/2009	D-Devrinol 450 SC: acute dermal toxicity study in rats Company Report No.: D03515 Harlan Laboratories Ltd., Switzerland GLP, Unpublished	None
CP 7.1.3/01	[redacted]	2011	D-Devrinol 450 SC: 4 hour acute inhalation toxicity study in the rat Company Report No.: D03526 [redacted] GLP, Unpublished	Y	Y	Data protection is claimed in accordance with Article 59 of Regulation (EC) No 1107/2009	D-Devrinol 450 SC: 4 hour acute inhalation toxicity study in the rat Company Report No.: D03526 Harlan Laboratories Ltd., Switzerland GLP, Unpublished	None
CP	[redacted]	2010c	D-Devrinol 450 SC: primary skin	Y	Y	Data	D-Devrinol 450 SC:	None

7.1.4/01			irritation study in rabbits (4 hour semi-occlusive application) Company Report No.: D03537 [redacted] GLP, Unpublished			protection is claimed in accordance with Article 59 of Regulation (EC) No 1107/2009	primary skin irritation study in rabbits (4 hour semi-occlusive application) Company Report No.: D03537 Harlan Laboratories Ltd., Switzerland GLP, Unpublished	
CP 7.1.5/01	[redacted]	2011	D-Devrinol 450 SC: primary eye irritation study in rabbits. Company Report No.: D03548 [redacted] GLP, Unpublished	Y	Y	Data protection is claimed in accordance with Article 59 of Regulation (EC) No 1107/2009	D-Devrinol 450 SC: primary eye irritation study in rabbits. Company Report No.: D03548 Harlan Laboratories Ltd., Switzerland GLP, Unpublished	None
CP 7.1.6/01	[redacted]	2011	Local lymph node assay (LLNA) in mice with D-Devrinol 450 SC Company Report No.: 1365301 [redacted] GLP, Unpublished	Y	Y	Data protection is claimed in accordance with Article 59 of Regulation (EC) No 1107/2009	Local lymph node assay (LLNA) in mice with D-Devrinol 450 SC Company Report No.: 1365301 Harlan Cytotest Cell Research GmbH (Harlan CCR), Germany GLP, Unpublished	None
CP 7.3.1/01	Johnson, I.R.	2014	Napropamide-M 450 g/L SC – *in vitro* absorption through human dermatomed skin using [^{14}C]-napropamide-M. Company Report No.: JV2242-REG Dermal Technology Laboratory Ltd., UK GLP, Unpublished	N	Y	Data protection is claimed in accordance with Article 59 of Regulation (EC) No 1107/2009	Napropamide-M 450 g/L SC – *in vitro* absorption through human dermatomed skin using [^{14}C]-napropamide-M. Company Report No.: JV2242-REG Dermal Technology Laboratory Ltd., UK GLP, Unpublished	None

APPENDIX 1: OPERATOR EXPOSURE CALCULATIONS

Estimate 1: German model estimate of exposure for operators applying 'D-Devrinol 450-SC': field crop sprayer - no PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Product	**D-Devrinol**		Active substance	**Napromamide M**	
Formulation type	Liquid		a.s. concentration	**450**	g/l
Dermal absorption from product	**0.6**	%	Dermal absorption from spray	**18**	%
RPE during mix/loading	None		RPE during application	None	
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	**1.7**	l product/ha	Work rate/day	**20**	ha

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2.4	mg/kg a.s.
Hand contamination/day	36.72	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	36.72	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0.0006	mg/kg a.s.
Inhalation exposure/day	0.00918	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.00918	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed boom sprayer: hydraulic nozzles

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	0.06	0.38	1.6	
Dermal contamination/day	0.918	5.814	24.48	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	31.212	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0.001	mg/kg a.s.
Inhalation exposure/day	0.0153	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.0153	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	36.72	mg/day	31.212	mg/day
Percent absorbed	0.6	%	18	%
Absorbed dose (dermal route)	0.22032	mg/day	5.61816	mg/day
Inhalation exposure to a.s.	0.00918	mg/day	0.0153	mg/day
Total systemic exposure	0.2295	mg/day	5.63346	mg/day

PREDICTED EXPOSURE

Total systemic exposure	5.86296	mg/day
Operator body weight	70	kg
Operator exposure	0.083756571	mg/kg bw/day
AOEL	0.5	mg/kg bw/day
% AOEL	16.75131429	

Estimate 2: UK POEM estimate of exposure for operators applying 'D-Devrinol 450-SC': field crop sprayer - no PPE

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Product	**D-Devrinol**		Active substance	**Napromamide M**	
Formulation type	water-based		a.s. concentration	**450**	mg/ml
Dermal absorption from product	**0.6**	%	Dermal absorption from spray	**18**	%
Container	10 litres 63 mm closure				
PPE during mix/loading	None		PPE during application	None	
Dose	**1.7**	l/ha	Work rate/day	**50**	ha
Application volume	**200**	l/ha	Duration of spraying	**6**	h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	1.7	litres product/ha
Work rate	50	ha/day
Number of operations	9	/day
Hand contamination	0.45	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	0.45	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	200	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65%	10%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	5%	15%	
Dermal exposure	6.5	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	41.55	ml/day		

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0.45	ml/day	41.55	ml/day
Concen. of a.s. product or spray	450	mg/ml	3.825	mg/ml
Dermal exposure to a.s.	202.5	mg/day	158.92875	mg/day
Percent absorbed	0.6	%	18	%
Absorbed dose	1.215	mg/day	28.607175	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	3.825	mg/ml
Inhalation exposure to a.s.	0.2295	mg/day
Percent absorbed	100	%
Absorbed dose	0.2295	mg/day

PREDICTED EXPOSURE

Total absorbed dose	30.051675	mg/day
Operator body weight	60	kg
Operator exposure	0.50086125	mg/kg bw/day
AOEL	0.5	mg/kg bw/day
% AOEL	100.17225	

Estimate 3: UK POEM estimate of exposure for operators applying 'D-Devrinol 450-SC': field crop sprayer / gloves during mixing and loading

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Product	**D-Devrinol**		Active substance	**Napromamide M**
Formulation type	water-based		a.s. concentration	**450** mg/ml
Dermal absorption from product	**0.6** %		Dermal absorption from spray	**18** %
Container	10 litres 63 mm closure			
PPE during mix/loading	Gloves		PPE during application	None
Dose	**1.7** l/ha		Work rate/day	**50** ha
Application volume	**200** l/ha		Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	1.7	litres product/ha
Work rate	50	ha/day
Number of operations	9	/day
Hand contamination	0.45	ml/day
Protective clothing	Gloves	
Transmission to skin	5	%
Dermal exposure to formulation	0.0225	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	200	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65%	10%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	5%	15%	
Dermal exposure	6.5	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	41.55	ml/day		

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0.0225	ml/day	41.55	ml/day
Concen. of a.s. product or spray	450	mg/ml	3.825	mg/ml
Dermal exposure to a.s.	10.125	mg/day	158.92875	mg/day
Percent absorbed	0.6	%	18	%
Absorbed dose	0.06075	mg/day	28.607175	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	3.825	mg/ml
Inhalation exposure to a.s.	0.2295	mg/day
Percent absorbed	100	%
Absorbed dose	0.2295	mg/day

PREDICTED EXPOSURE

Total absorbed dose	28.897425	mg/day
Operator body weight	60	kg
Operator exposure	0.48162375	mg/kg bw/day
AOEL	0.5	mg/kg bw/day
% AOEL	96.32475	

Estimate 4: German (BfR) estimate of bystander exposure to spray drift

Estimation of bystander exposure during/after application in Field Crops, Tractor Mounted

Input parameters considered for the estimation of bystander exposure:

Intended use(s):	OSR and brassica vegetables		**Drift (D):**	0.29	% (FCTM, 10 m)
Application rate (AR):	0.765	kg a.s./ha	**Exposed Body Surface Area (BSA):**	1	m² (adults)
				0.21	m² (children)
Body weight (BW):	60	kg/person (adults)	**Specific Inhalation Exposure (I^*_A):**	0.001	mg/kg a.s. (6 hours, adults)
	16.15	kg/person (children)		0.00057	mg/kg a.s. (6 hours, children)
Dermal absorption (DA):	18.00	% ('worst case')	**Area Treated (A):**	20	ha/d (based on Field Crops, Tractor Mounted (FCTM))
Inhalation absorption (IA):	100	%	**Exposure duration (T):**	5	min
AOEL:	0.5	mg/kg bw/d			

Bystander exposure towards Napropamide-M					
Adults			**Children**		
Bystander: Dermal exposure after application in OSR and brassica vegetables (via spray drift)					
SDE_B = (AR x D x BSA x DA) / BW			SDE_B = (AR x D x BSA x DA) / BW		
(76.5 x 0.29% x 1 x 18%) / 60			(76.5 x 0.29% x 0.21 x 18%) / 16.15		
External exposure	0.22185	mg/person	External exposure	0.0465885	mg/person
External exposure	0.0036975	mg/kg bw/d	External exposure	0.00288474	mg/kg bw/d
Absorbed dose:	**0.000666**	**mg/kg bw/d**	**Absorbed dose:**	**0.0005193**	**mg/kg bw/d**
Bystander: Inhalation exposure after application in OSR and brassica vegetables					
SIE_B = (I^*_A x AR x A x T x IA) / BW			SIE_B = (I^*_A x AR x A x T x IA) / BW		
(0,000 / 360 x 0.765 x 20 x 5 x 100%) / 60			(0,000 / 360 x 0.765 x 20 x 5 x 100%) / 16.15		
External exposure	0.0002125	mg/person	External exposure	0.00012213	mg/person
External exposure	3.5417E-06	mg/kg bw/d	External exposure	7.562E-06	mg/kg bw/d
Absorbed dose:	**0.000004**	**mg/kg bw/d**	**Absorbed dose:**	**0.000008**	**mg/kg bw/d**
Total systemic exposure: SE_B = SDE_B + SIE_B			Total systemic exposure: SE_B = SDE_B + SIE_B		
Total systemic exposure (absorbed dose)	0.0401455	mg/person	Total systemic exposure (absorbed dose)	0.00850806	mg/person
Total systemic exposure (absorbed dose)	**0.000669**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.000527**	**mg/kg bw/d**
% of AOEL:	**0.13**	**%**	**% of AOEL:**	**0.11**	**%**

Estimate 5: German (BfR) estimate of resident exposure to spray drift

Estimation of resident exposure after application in Field Crops, Tractor Mounted (FCTM)

Input parameters considered for the estimation of resident exposure:

Intended use(s):	OSR and brassica vegetables		**Drift (D):**	0.29	% (FCTM, 10 m)
Application rate (AR):	0.765	kg a.s./ha	**Transfer coefficient (TC):**	7300	cm^2/h (adults)
				2600	cm^2/h (children)
Number of applications (NA):	1		**Turf Transferable Residues (TTR):**	5	%
Body weight (BW):	60	kg/person (adults)	**Exposure Duration (H):**	2	h
	16.15	kg/person (children)	**Airborne Concentration of Vapour (ACV):**	0.001	mg/m3
Dermal absorption (DA):	18.00	% ('worst case')	**Inhalation Rate (IR):**	16.57	m^3/d (adults),
Inhalation absorption (IA):	100	%		8.31	m^3/d (children)
Oral absorption (OA)	100	%	**Saliva Extraction Factor (SE):**	50	%
AOEL	0.5	mg/kg bw/d	**Surface Area of Hands (SA):**	20	cm^2
			Frequency of Hand to Mouth (Freq):	20	events/h
			Dislodgeable foliar residues (DFR):	20	%
			Ingestion Rate for Mouthing of Grass/Day (IgR):	25	cm^2/d

Resident exposure towards Napropamide-M					
Adults			**Children**		
Residents: Dermal exposure after application in OSR and brassica vegetables (via deposits caused by spray drift)					
SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW			SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW		
(0.00765 x 1 x 0.29% x 5% x 7300 x 2 x 18%) / 60			(0.00765 x 1 x 0.29% x 5% x 2600 x 2 x 18%) / 16.15		
External exposure	0.01619505	mg/person	External exposure	0.0057681	mg/person
External exposure	0.00026992	mg/kg bw/d	External exposure	0.00035716	mg/kg bw/d
Absorbed dose:	**0.000049**	**mg/kg bw/d**	**Absorbed dose:**	**0.0000643**	**mg/kg bw/d**
Residents: Inhalation exposure to vapour					
SIE_R = (AC_V x IR x IA) / BW			SIE_R = (AC_V x IR x IA) / BW		
(0.001 x 16.57 x 100%) / 60			(0.001 x 8.31 x 100%) / 16.15		
External exposure	0.01657	mg/person	External exposure	0.00831	mg/person
External exposure	0.00027617	mg/kg bw/d	External exposure	0.00051455	mg/kg bw/d
Absorbed dose:	**0.0002762**	**mg/kg bw/d**	**Absorbed dose:**	**0.0005146**	**mg/kg bw/d**
			Residents: Oral exposure (hand-to-mouth transfer)		
			SOE_H = (AR x NA x D x TTR x SE x SA x Freq x H x OA) /		
			(0.00765 x 1 x 0.29% x 5% x 50% x 20 x 20 x 2 x 100%) /		
			External exposure	0.0004437	mg/person
			External exposure	2.7474E-05	mg/kg bw/d
			Absorbed dose	**0.0000275**	**mg/kg bw/d**
			Residents: Oral exposure (object-to-mouth transfer)		
			SOE_O = (AR x NA x D x DFR x IgR x OA) / BW		
			(0.00765 x 1 x 0.29% x 20% x 25 x 100%) / 16.15		
			External exposure	0.00011093	mg/person
			External exposure	6.8684E-06	mg/kg bw/d
			Absorbed dose	**0.000007**	**mg/kg bw/d**
Total systemic exposure: SE_R = SDE_R + SIE_R			Total systemic exposure: SE_R = SDE_R + SIE_R + SOE_H + SOE_O		
Total systemic exposure (absorbed dose)	0.01948511	mg/person	Total systemic exposure (absorbed dose)	0.00990288	mg/person
Total systemic exposure (absorbed dose)	**0.0003248**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0006132**	**mg/kg bw/d**
% of AOEL:	**0.06**	**%**	**% of AOEL:**	**0.12**	**%**