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Oxamyl 10GR

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ANNEX B.6
Toxicology and metabolism data and assessment of risks for humans

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Date	Data points containing amendments or additions	Document identifier or version number
May 2016	First RAR of Italy	
December 2017	Revised RAR after comment CoRMS (France)	

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

Introduction

Oxamyl 10GR was the representative formulation for the first approval review of oxamyl.

This document addresses the CP 7 data requirements (mammalian toxicology) related to Oxamyl 10GR.

Test substance specification can be determined from the test substance code, which is a research and development code number given to a specific batch of produced material (either technical or formulated). The approximate composition of the material(s) used in the various tests is given in Table 1.

Table 1 Test substance specification

Test substance	Lot/Batch code	Type	Composition
2001 submission			
Oxamyl 10GR	D1410-377	Granular formulation (GR)	100 g oxamyl/kg
Oxamyl 10GR	D1410-377A	Granular formulation (GR)	100 g oxamyl/kg
Oxamyl 10GR	D1410-377B	Granular formulation (GR)	100 g oxamyl/kg
Oxamyl 10GR	D1410-395	Granular formulation (GR)	100 g oxamyl/kg

The composition of Oxamyl 10GR used in the toxicological studies is provided in Oxamyl RAR Vol-4.

Unless specifically indicated, all reports in this section are submitted to address mandatory data requirements for the approval of active substance.

Unless specifically indicated, all tests submitted in this section, which involve vertebrate animals, address mandatory data requirements which could not be met with alternative methods. Studies were conducted according to prescribed guidelines.

Unless specifically indicated, this section does not contain reports of studies duplicating previous tests on vertebrate animals.

B.6.1 Acute toxicity of plant protection product

A full battery of acute toxicity studies was conducted with Oxamyl 10GR. Summaries of these studies are presented below.

B.6.1.1 Oral toxicity

Study submitted in the EU Dossier in 2001 and included in the first EU approval review.

B.6.1.1/01

Reference: --	**Report**	[redacted] (1999); Oxamyl 10G: Acute oral toxicity study in male and female rats **DuPont Report No.:** DuPont-2703 **Guidelines:** 59 NohSan No. 4200 (1985), EEC Method B.1. (1992), OECD 401 (1987), U.S. EPA 870.1100 (1998) GLP: YES

1. Test material: Oxamyl 10GR
   Lot/Batch #: D1410-377
   Purity: 100 g a.s./kg

I. MATERIALS AND METHODS:

Oxamyl 10G contains 10% Oxamyl active ingredient (11.17% by analysis) and 90% inert ingredients. No known impurities. Batch DPX-D1410-377.

Single oral doses of Oxamyl 10 G were administered as a suspension in deionised water by gavage to fasted Crl:CD® (SD)IGS BR rats (5/sex/group) at dose levels of 35, 41, and 47 mg/kg bw for males and 22, 35, and 47 mg/kg bw for females. Observations for mortality and signs of illness, injury and abnormal behaviour were made daily throughout the study. Rats were weighed and observed for clinical signs of toxicity daily (excluding weekends unless warranted by the condition of the rat). Surviving rats were observed for 14 days following dose administration. Rats found dead during the study or euthanised by design at the end of the study were submitted for a gross pathological examination.

II. RESULTS

All deaths occurred on the day of dosing except for one male from the 41 mg/kg bw group that was found dead on day 3 (Table 2).

Table 2 Acute oral toxicity of Oxamyl 10G to rats

Dose (mg/kg bw)	Mortality Ratio	Time of Death (hours after dosing)	No. of animals showing clinical signs of toxicity	LD_{50} (mg/kg bw) 14 days
MALE RATS				
35	0/5	-	5/5	43
41	2/5	within 24 hrs	5/5	
47	4/5	within 72 hrs	2/5	
FEMALE RATS				
22	0/5	-	5/5	34
35	3/5	within 24 hrs	2/5	
47	5/5	within 24 hrs	1/5	

Clinical signs most often observed include tremors, muscle fasciculations, clear oral discharge, and staining of various body parts. Other clinical signs included convulsions, diarrhoea, spasms, splayed hind limbs, gasping, irregular respiration, alopecia, lethargy, licking, lung noise, hunched over posture, ruffled fur, wet perineum or underbody and ocular discharge. Most clinical signs subsided by day 2 and, with the exception of alopecia, those clinical signs that persisted were no longer observed after day 6. Gross pathological changes were observed in certain animals (e.g. kidney dilation, chromodacryorrhea of the skin) but were considered non-specific and not indicative of target organ toxicity.

Weight loss of up to 15% occurred in most of the surviving rats by day 3 or 4 but they began gaining weight by day 4 or 5 and surpassed their initial body weight by day 9 or sooner.

III. CONCLUSIONS

The acute oral median lethal dose of Oxamyl 10G is estimated to be 43 mg/kg bw for male rats and 34 mg/kg bw for females. Therefore the formulation classifies as toxic by the oral route.

The oral toxicity study DuPont-2703, originally submitted under EU Rev8 Point IIIA 7.1.1 and conducted with test material Oxamyl 10GR, was conducted under guidelines 59 NohSan No. 4200 (1985), EEC Method B.1. (1992), OECD 401 (1987), and U.S. EPA 870.1100 (1998). A review of this study indicates that it fully meets the current guideline (EEC Method B.1).

RMS comments and conclusions for the renewal: **The study is acceptable as a key study**

B.6.1.2 Dermal toxicity

Study submitted in the EU Dossier in 2001 and included in the first EU approval review.

B.6.1.2/01

Reference: --	**Report**	[redacted] (1999); Oxamyl 10G: Acute dermal toxicity study in rats **DuPont Report No.:** DuPont-2810 **Guidelines:** OECD 402 (1987), EEC Method B.3. (1992), 59 NohSan No. 4200 (1985), U.S. EPA 870.1200 (1998) GLP:YES

1. Test material: Oxamyl 10GR
   Lot/Batch #: D1410-377
   Purity: 100 g a.s./kg

Deviations: Based on OECD test guideline 402 the following deviations were identified in the study protocol:-

- ± 20% weight variation on test day 0 was not determined.

I. MATERIALS AND METHODS:

Oxamyl 10G contains 10% Oxamyl active ingredient (10.0% by analysis) and 90% inert ingredients. No known impurities. Batch DPX-D1410-377. It was ground into a powder for this study.

A limit test using a dose of 5000 mg/kg bw Oxamyl 10G was carried out in a group of 5 male and 5 female fasted Crl:CD® (SD)IGS BR rats. Initially, an attempt was made to apply the test substance as a paste (mixed with 0.8 mL of deionised water) directly to the closely shaven test site (5 cm x 7.4 cm) of one male rat. However, it did not make good contact with the skin. Therefore, for the remaining 9 rats, the test substance was applied to a 2-ply gauze square (approximately 37 cm^2) that was pre-moistened in deionised water. The gauze pad was, in turn, applied to the closely-shaven test sites on the animals and held in place for 24 hours with successive layers of stretch gauze bandage and self adhesive bandage. The rats were fitted with plastic collars to prevent ingestion of the test substance or disruption of the dressing.

Observations during the 15 day test period included daily mortality checks and daily observations for clinical signs of toxicity and dermal irritation (excluding weekends) and body weight determinations on test days 1, 2, 8 and 15. All rats were necropsied on day 15 and submitted for a gross pathological examination.

Note: the wrappings of 1 male and 1 female rat became dislodged during the exposure period. These 2 animals were removed from the study since they did not receive 24 hours exposure and 1 additional male and 1 additional female were dosed as replacements. The data for the rat that had the test substance applied directly to its skin was also not used in determining the LD_{50} of the test substance and was excluded from the summary of results due to uncertainties as to whether or not the rat had an adequate exposure.

II. RESULTS

No deaths occurred and no clinical signs of toxicity were observed during the study (Table 3).

Table 3 Acute dermal toxicity of Oxamyl 10G to rats

Dose (mg/kg bw)	Mortality Ratio	No. of animals showing clinical signs of toxicity	LD_{50} (mg/kg bw) 14 days
Males			
5000	0/4	0/4	>5000
Females			
5000	0/5	0/5	>5000

Slight to moderate erythema was observed in 4 rats (1 female, 3 males), and slight oedema was observed in 2 male rats. All signs of dermal irritation had disappeared by day 5. Body weight losses of approximately 4 to 10% of the initial body weight occurred in most rats by the day after application (day 2). This weight loss was attributed in part to stress associated with the wrapping procedure as all animals recovered from this initial loss in body weight by day 8. No gross lesions were observed on necropsy.

III. CONCLUSIONS

The acute dermal median lethal dose of Oxamyl 10G is estimated to be > 5000 mg/kg bw for both male and female Sprague Dawley rats.

The dermal toxicity study DuPont-2810, originally submitted under EU Rev8 Point IIIA 7.1.2 and conducted with test material Oxamyl 10GR, was conducted under guidelines OECD 402 (1987), EEC Method B.3. (1992), 59 NohSan No. 4200 (1985), and U.S. EPA 870.1200 (1998). A review of this study indicates that it fully meets the current guideline (EEC Method B.3), being the deviation only minor and not considered to affect the outcome of the study. Therefore, Oxamyl 10G does not classify via the dermal route.

RMS comments and conclusion for the renewal:

The study is acceptable as a key study

B.6.1.3 Inhalation toxicity

Study submitted in the EU Dossier in 2001 and included in the first EU approval review.

B.6.1.3/01

Reference: --	**Report**	[redacted] (1999); Oxamyl 10G: Inhalation lethal concentration (LC_{50}) study in rats **DuPont Report No.:** DuPont-1987 **Guidelines:** 59 NohSan No. 4200 (1985), OECD 403 (1981), EEC Method B.2. (1992), OPPTS 870.1300 (1998) GLP: YES

1. Test material: Oxamyl 10GR
   Lot/Batch #: D1410-377A
   Purity: 100 g a.s./kg

Deviations: Based on OECD test guideline 403, no guideline deviations were identified.

I. MATERIALS AND METHODS

Oxamyl 10G was milled by the sponsor to a fine powder (median particle size 6.5 µm) and assigned batch reference no. DPX-D1410-377A. The Oxamyl composition was 10% (11.7% by analysis) with 90% inert ingredients. No known impurities.

Four groups of 5 male and 5 female Crl:CD® (SD)IGS BR rats were exposed nose-only to a dust atmosphere of Oxamyl 10G for a single 4-hour exposure. The concentration levels were 0.39, 0.52, 0.62, or 0.73 mg/L. The MMAD was 2.6 - 3.0 µm. The chamber dust concentration was measured by gravimetric analysis of filters at approximately 45-minute intervals during each exposure and the concentration of active ingredient was measured by high performance liquid chromatography. Two samples to determine particle size distribution were taken during each exposure. The chamber airflow and the chamber temperature were determined at approximately 30-minute intervals and the relative humidity and chamber oxygen concentrations were recorded 3 times during each exposure period.

Rats were observed for mortality and response to alerting stimuli during the exposure and observed for mortality and clinical signs of toxicity immediately after they were removed from the restrainers following exposure. During a 14-day recovery period, all surviving rats were checked each day for mortality. Clinical observations and bodyweights were recorded daily for the first 5 days of the study and then once per week thereafter throughout the post- exposure period. At the end of the recovery period, all rats were sacrificed and subjected to gross pathological examination.

II. RESULTS

The achieved test atmosphere characteristics are summarised in Table 4. The test substance was considered to be homogeneously distributed throughout the exposure chamber. The test atmosphere was considered to be respirable in rats. The calculated mean percentage of active ingredient for the dust collected on the filters was approximately 13% and therefore remained essentially unchanged from the supplied formulation when generated into the exposure chamber. Airflow during the exposures was maintained at approximately 35 L/min. Chamber relative humidity ranged from 45 - 61% and the chamber oxygen concentration was 21%. The measured chamber temperature (23 - 26ºC) was slightly outside the targeted range (20 - 24ºC) but was considered to be acceptable for the conduct of the study.

Table 4 Chamber Atmosphere Analysis

Chamber Atmospheric Concentration (mg/L)		**MMAD (µm)**	**GSD**	**% Particles by Mass**		
Mean	**SD**			**< 1 µm**	**< 3 µm**	**< 10 µm**
0.39	0.047	3.0 2.7	2.1 2.1	7.5 10	49 56	94 96
0.52	0.14	2.6 2.7	2.0 2.1	8.8 11.0	56 55	96 95
0.62	0.099	2.6 2.6	2.1 2.1	10 10	57 56	96 96
0.73	0.25	2.8 2.8	2.1 1.9	7.8 6.6	53 53	95 96

SD, Standard Deviation; MMAD, Mass Median Aerodynamic Diameter 2 Separate Measurements; GSD, Geometric Standard Deviation 2 Separate Measurements

Deaths occurred at all but the lowest exposure concentration. All mortalities occurred during the exposure period..

Table 5 Acute inhalation toxicity of Oxamyl 10G to rats

Exposure Concentration (mg/kg bw)	Mortality Ratio	Time of Death (hours after dosing)	No. of animals showing clinical signs of toxicity	LC_{50} (mg/L) 14 days
Males				0.68*
0.39	0/5	-	5/5	
0.52	0/5	-	5/5	
0.62	2/5	during exposure	3/3	
0.73	2/5	during exposure	3/3	
Females				
0.39	0/5	-	5/5	
0.52	1/5	during exposure	4/4	
0.62	2/5	during exposure	3/3	
0.73	4/5	during exposure	1/1	

* 95% confidence interval = 0.61 to 0.87 mg/L

No abnormal clinical signs were observed in rats during the exposure period but upon removal from the chamber, tremors, muscle fasciculation, abnormal gait/mobility, immobility, salivation, nasal/ocular discharge, wet/stained perineum, and gasping were recorded. Other clinical signs observed up to day 5 of the recovery period included hunched posture, nasal/ocular discharge, wet/stained perineum, lethargy, stained fur, and ruffled fur. Corneal opacity was seen in one male exposed to 0.73 mg/L from days 2 - 15.

Moderate to severe body weight losses were noted in surviving male rats the day following exposure (5.4% - 15% of initial body weight). Male rats continued to show slight to moderate body weight losses up to 4 days after exposure. Slight to severe body weight losses were noted in surviving female rats the day following exposure (2.4% - 13% of initial body weight). Occasional weight losses were seen in some surviving females (dosed at 0.39 or 0.52 mg/L) throughout the remainder of the 14-day recovery period. However, all rats showed overall weight gain by the end of the recovery period.

The gross observations were non-specific and not indicative of target organ toxicity.

III. CONCLUSIONS

Under the conditions of the study, the four-hour LC50 for Oxamyl 10G in male and female Sprague Dawley rats was estimated to be 0.68 mg/L. Therefore, Oxamyl 10G classifies as toxic via inhalation.

The inhalation toxicity study DuPont-1987, originally submitted under EU Rev8 Point IIIA 7.1.3 and conducted with test material Oxamyl 10GR, was conducted under guidelines 59 NohSan No. 4200 (1985), OECD 403 (1981), EEC Method B.2. (1992), and OPPTS 870.1300 (1998). A review of this study indicates that it fully meets the current guideline (EEC Method B.2).

RMS comments and conclusion for the renewal:

The study is acceptable as a key study

B.6.1.4 Skin irritation

Study submitted in the EU Dossier in 2001 and included in the first EU approval review.

B.1.4/01

Reference: --	**Report**	[redacted] (1999); Oxamyl 10G: Primary dermal irritation study in rabbits **DuPont Report No.:** DuPont-2453 **Guidelines:** OECD 404 (1992), 59 NohSan No. 4200 (1985), EEC Method B.4.

		(1992), U.S. EPA 870.2500 (1998) GLP: YES

1. Test material: Oxamyl 10GR
   Lot/Batch #: D1410-377
   Purity: 100 g a.s./kg

Deviations: Based on OECD test guideline 404, no guideline deviations were identified.

I. MATERIALS AND METHODS:

Oxamyl 10G was milled to a fine powder and assigned batch reference no. DPX-D1410- 377A. The Oxamyl composition was 10% (10.0% by analysis) with 90% inert ingredients. No known impurities.

A group of 6 male HM:(NZW)fBR New Zealand White albino rabbits received a single 4- hour application of 0.5 g of test substance, moistened with a small amount (0.4 mL) of deionised water, to a closely-shaven test site (approximately 6 cm^2) on the back of each animal. The test substance was covered with a 4-ply, 1inch gauze square and held in place with non-irritating tape, which was then wrapped in rubber sheeting. The rabbits were placed in stocks during the 4-hour exposure period.

Approximately 1 hour after removal of the test patches, the test sites were evaluated for erythema, oedema and other evidence of dermal effects, and were scored according to the Draize scale. Additional evaluations were made approximately 24, 48 and 72 hours after removal of the patches (Table 6). Adjacent areas of untreated skin were used for comparison. Mean Group scores were calculated for each dermal response (erythema and oedema) by summing the scores obtained from all animals at the 24-, 48- and 72-hour observations. The 3 means corresponding to the 3 observation periods were averaged and overall averages were obtained for each dermal response.

The rabbits were also examined for clinical signs of toxicity at each dermal evaluation and their weights were recorded on the day of treatment and at the last dermal evaluation (72 hours).

II. RESULTS

Two of the six rabbits exhibited slight erythema (score of 1 or 2) at 24 hours (Table 6). One of these rabbits also exhibited desquamation at 24 hours. No dermal irritation was observed in the other four rabbits. No oedema, significant weight loss, or clinical signs of toxicity were observed.

Table 6 Oxamyl 10G - Individual and Mean Skin Irritation Scores (Draize Scale) in the Rabbit

Rabbit Number	Hours After Test Substance Removal							
	Erythema				Oedema			
	1	24	48	72	1	24	48	72
33526	0	0	0	0	0	0	0	0
33527	0	0	0	0	0	0	0	0
33528	0	2	0	0	0	0	0	0
33529	0	0	0	0	0	0	0	0
33530	0	1	0	0	0	0	0	0
33533	0	0	0	0	0	0	0	0
Mean		**0.5**	**0**	**0**		**0**	**0**	**0**
Overall average: (24hr + 48hr + 72hr) / 3		**0.17**				**0.00**		

The overall average mean values for erythema and oedema formation were 0.17 and 0.0, respectively.

III. CONCLUSIONS

Under the conditions of test, Oxamyl 10G is not irritating to rabbit skin and does not require labelling as a dermal irritant.

The skin irritation study DuPont-2453, originally submitted under EU Rev8 Point IIIA 7.1.4 and conducted with test material Oxamyl 10GR, was conducted under guidelines OECD 404 (1992), 59 NohSan No. 4200 (1985), EEC Method B.4. (1992), and U.S. EPA 870.2500 (1998). A review of this study indicates that it fully meets the current guideline (EEC Method B.4).

RMS comments and conclusion for the renewal:

The study is acceptable as a key study

B.6.1.5 Eye irritation

Study submitted in the EU Dossier in 2001 and included in the first EU approval review.

B.6.1.5/01

Report	[redacted] (1999); Oxamyl 10G: Primary eye irritation study in rabbits **DuPont Report No.:** DuPont-2640 **Guidelines:** OECD 405 (1987), EEC Method B.5. (1992), 59 NohSan No. 4200 (1985), U.S. EPA 870.2400 (1998) GLP: YES

1. Test material: Oxamyl 10GR
   Lot/Batch #: D1410-377B
   Purity: 100 g a.s./kg

Deviations: Based on OECD test guideline 405, no guideline deviations were identified.

I. MATERIALS AND METHODS

DPX-D1410-377 was milled for eye testing and assigned batch reference no. DPX-D1410- 377B. The Oxamyl composition was 10% (10.0% by analysis) with 90% inert ingredients. No known impurities.

Oxamyl 10G was applied undiluted to the lower conjunctival sac of the right eye of 6 male New Zealand White rabbits at a rate of 44 mg test substance/animal (a weight equivalent to a volume of 0.1 mL). The eye was not washed following treatment. The left eye of each rabbit remained untreated and served as a control. Rabbits were examined for ocular irritation approximately 1, 24, 48, and 72 hours and 7 days after instillation. At each of these observation periods, eyes were examined using illumination and magnification and the conjunctiva, iris and cornea were scored for ocular reactions according to the Draize scale. Flourescein stain examinations for corneal injury were conducted at 24, 48, and 72 hours following instillation. The animals were weighed on the day of treatment and at the last ocular evaluation.

II. RESULTS

All animals pawed their treated eyes immediately after instillation of the test substance. The pupils of the treated eyes of all rabbits were constricted at the 1-hour observation only. The pupils of the control eyes of all rabbits were normal. Iritis (score of 1), conjunctival redness (score of 1, 2 or 3), chemosis (score of 1 or 2) and discharge (score of 3) were noted in all rabbits (Table 7). In addition, flourescein stain examinations were positive for corneal opacity (score of 2) in three rabbits and iritic flare was observed in two rabbits. The treated

eyes of all animals were normal by day 7. One rabbit had lost approximately 2% of its initial body weight by day 7.

Table 7 Oxamyl 10G - Individual and Mean Eye Irritation Scores (Draize Scale) in the Rabbit

Rabbit No.	Hours After Test Substance Removal															
	Corneal Opacity*				Iritis				Conjunctival Redness				Conjunctival Chemosis			
	1	24	48	72	1	24	48	72	1	24	48	72	1	24	48	72
33552	0	0	0	0	1	0	0	0	2	2	2	1	1	1	0	0
33555	0	2	2	0	1	1 F	0	0	2	2	2	1	1	2	1	0
33531	0	2	2	0	1	0F	0	0	2	3	2	1	1	2	1	0
33532	0	0	0	0	1	0	0	0	1	2	2	1	1	1	1	1
33535	0	0	0	0	1	0	0	0	1	2	1	1	1	1	0	0
33541	0	2	2	0	1	1	0	0	1	2	1	1	1	1	1	1
Mean		**1**	**1**	**0**		**0.33**	**0**	**0**		**2.17**	**1.67**	**1**		**1.33**	**0.67**	**0.33**
Average of Means		**0.67**				**0.11**				**1.61**				**0.78**		

* All cases of positive corneal opacity were determined using Flourescein Stain.
F Iritic Flare

III. CONCLUSIONS

Under the conditions of the study, Oxamyl 10G is not irritating to the rabbit eye and does not require labelling as an eye irritant. The eye irritation study DuPont-2640, originally submitted under EU Rev8 Point IIIA 7.1.5 and conducted with test material Oxamyl 10GR, was conducted under guidelines OECD 405 (1987), EEC Method B.5. (1992), 59 NohSan No. 4200 (1985), and U.S. EPA 870.2400 (1998). A review of this study indicates that it fully meets the current guideline (EEC Method B.5).

RMS comments and conclusion for the renewal:

The study is acceptable as a key study

B.6.1.6 Skin sensitisation

Study submitted in the EU Dossier in 2001 and included in the first EU approval review.

B.6.1.6/01

Report	[redacted] (1999); Vydate 10G: Evaluation of the potential dermal sensitization in the Guinea pig (modified Buehler method) **DuPont Report No.:** DuPont-1953 **Guidelines:** EEC Method B.6. (1992), OECD 406 (1992), 59 NohSan No. 4200 (1985), U.S. EPA 81-6 (1982) GLP:YES

1. Test material: Oxamyl 10GR
   Lot/Batch #: D1410-377
   Purity: 100 g a.s./kg

Deviations: Based on OECD test guideline 406 the following deviations were identified in the study protocol:-

- The challenge application was conducted on test day 29 instead of day 28.

- Observation of skin sites following the challenge application was made approximately 24 and 48 hours after application instead of 30 and 54 hours after application.
- The relative humidity and temperature during the study were outside the recommended range but this is not believed to have affected results.

NOTE: The wrong certificate of analysis was supplied with the study [the certificate supplied was for Vydate Liquid (D1410-381) and not Vydate solid (D1410-377), as tested].

I. MATERIALS AND METHODS

Vydate 10G was assigned batch reference no. DPX-D1410-377. The Oxamyl composition was 10% (10.0% by analysis) with 90% inert ingredients. No known impurities. The substance was ground to a powder prior to testing.

Induction phase:

Following a dose range-finding study, a 0.5 g aliquot of Vydate 10G moistened with 0.5 mL of polyethylene glycol (PEG) was applied to the shaved back (left flank) of each of 20 male Hartley guinea pigs using a 25 mm Hill Top Chamber and covered with an occlusive wrapping. The test material was applied once a week at 7-day intervals for three weeks. The duration of each exposure was 6 hours, after which bandages and patches were removed and the test sites were wiped with PEG, followed by deionised water. The same procedure was conducted using a control group of 10 animals except that the test article was replaced by PEG. A positive control group was not run concurrently with the test material. However, the laboratory validated the testing procedures periodically using α-hexylcinnamaldehyde (technical grade 85%). Test sites were scored for dermal irritation at 24 and 48 hours after treatment.

Challenge phase:

Two weeks after the last induction treatment, challenge applications (0.5 g test material in 0.5 mL of PEG) were made on the right flank of the 20 test animals. The control animals were challenged with PEG only on the left flank and 0.5 g test material in 0.5 mL of PEG on the right flank. As before, the treated areas were covered with occlusive dressing for 6-hours, after which bandages and patches were removed and the test sites were wiped with PEG followed by deionised water. Dermal irritation or signs of sensitisation were scored at 24 and 48 hours after the challenge application.

II. RESULTS

Induction phase:

No dermal irritation was observed in test or the vehicle control animals (Table 8). Exfoliation and necrosis (with or without erythema) were observed in the positive control animals following the second and third induction applications (no responses were observed in the positive control animals after the first induction).

Challenge phase:

No dermal irritation was noted in the test or the vehicle control groups (Table 8). The positive control, α-hexylcinnamaldehyde, produced slight to moderate erythema at the 24- and/or 48-hour scoring intervals. Only 2 animals had no reaction at 24 or 48 hours when challenged with the positive control.

Table 8 Oxamyl: dermal irritation/sensitisation scores

Response	Oxamyl 10 GR				Propylene Glycol				α-hexylcinnamaldehyde			
	Induction		Challenge		Induction		Challenge		Induction		Challenge	
	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
No reaction	20/20	20/20	19/19*	19/19	10/10	10/10	10/10	10/10	5/20	2/20	3/20	10/20
Erythema	0/20	0/20	0/19	0/19	0/10	0/10	0/10	0/10	4/20	5/20	17/20	10/20
Oedema	0/20	0/20	0/19	0/19	0/10	0/10	0/10	0/10	0/20	0/20	0/20	0/20
Exfoliation	0/20	0/20	0/19	0/19	0/10	0/10	0/10	0/10	8/20	9/20	0/20	0/20
Necrosis	0/20	0/20	0/19	0/19	0/10	0/10	0/10	0/10	12/20	12/20	0/20	0/20

* For one animal, the patch slipped onto a furred area; therefore, the animal was not scored nor used in computation.

III. CONCLUSIONS

Based on the results of this study, Vydate 10G containing 10% Oxamyl is not a skin sensitiser.

The skin sensitisation study DuPont-1953, originally submitted under EU Rev8 Point IIIA 7.1.6 and conducted with test material Oxamyl 10GR, was conducted under guidelines EEC Method B.6. (1992), OECD 406 (1992), 59 NohSan No. 4200 (1985), and U.S. EPA 81-6 (1982). A review of this study indicates that it fully meets the current guideline (EEC Method B.6).

RMS comments and conclusion for renewal:

The study is accepted as a key study

B.6.1.7 Supplementary studies on the plant protection product

No supplementary studies are required to satisfy the data requirements for registration of Oxamyl 10GR.

B.6.1.8 Supplementary studies for combinations of plant protection products

No supplementary studies are required to satisfy the data requirements for registration of Oxamyl 10GR.

B.6.1.9 Summary of acute toxicity

Table 9 Summary of acute toxicity data for Oxamyl 10GR

Type of study	Species	Results	Reference
Acute oral LD_{50}	Rat	LD_{50} = 34 mg/kg	DuPont-2703
Acute dermal LD_{50}	Rat	LD_{50} = >5000 mg/kg	DuPont-2810
Acute inhalation LC_{50} (4h)	Rat	LC_{50} = 0.68 mg/L	DuPont-1987
Skin irritation	Rabbit	Not irritating	DuPont-2453
Eye irritation	Rabbit	Not irritating	DuPont-2640
Skin sensitisation (Buehler test)	Guinea Pig	Not sensitising	DuPont-1953

Oxamyl 10GR was highly toxic by the oral route of exposure with an LD_{50} of 34 mg/kg bw. It was also found to be toxic by the inhalation route with an LC_{50} of 0.68 mg/L. In contrast, by the dermal route of exposure it was not toxic, as the LD_{50} was found to be >5000 mg/kg bw. Oxamyl 10GR was not irritating to the eyes or skin of rabbits and was found not to be a sensitiser in a modified Buehler study, which was conducted in lieu of the Guinea Pig Maximization study, as the material is highly toxic if dosed systemically.

In accordance with Regulation (EC) No. 1272/2008, classification of Oxamyl 10GR is required for acute oral, and inhalation toxicity. Acute oral Category 2 is applicable in accordance to Annex I - Part 3 - points 3.1.3 to 3.1.3.6.2.3 of Regulation (EC) No. 1272/2008 and its corresponding ATPs. Acute inhalation Category 3 is applicable in accordance to Annex I - Part 3 points 3.1.3 to 3.1.3.6.2.3 of Regulation (EC) No. 1272/2008 and its corresponding ATPs. Therefore, hazard statements

H300 Fatal if swallowed

H331 Toxic if inhaled

apply to Oxamyl 10GR. Classification for acute dermal, skin and eye irritation, and dermal sensitisation is not required.

B.6.2 Dermal absorption

Oxamyl 10GR was the representative formulation supporting the authorisation of oxamyl in the EU. The extent of absorption of oxamyl through skin was assessed in an *in vivo* dermal absorption study in rats and in a comparative *in vitro* dermal absorption study using rat and human skin. All relevant data are considered adequate.

B.6.2.1 Dermal absorption, *in vivo* in the rat

Study submitted in the EU Dossier in 2001 and included in the first EU approval review.

B.6.2.1/01

Reference: --	**Report**	[redacted] (1986); Dermal absorption of [^{14}C]-oxamyl in the rat **DuPont Report No.:** AMR 614-86 **Guidelines:** U.S. EPA 85-2 (1982) GLP: YES

1. Test material: [1-^{14}C]oxamyl
   Lot/Batch #: Not given
   Purity: radiopurity >99%

Deviations: Not applicable

I. **MATERIALS AND METHODS**

Radiolabelled ^{14}C-Oxamyl with a radiochemical purity greater > 99% was supplied and used as two separate dosing solutions :-

1. A high dose undiluted Vydate L formulation containing 48.6 mg Oxamyl per 200µl
2. A low dose Spray formulation containing 5.53 mg Oxamyl per 200µl.

Male Sprague-Dawley rats received a single dermal administration of either dosing solution, 12 rats per solution. Each dose group was subdivided into 2 groups of 6 rats each, which were used for serial blood sample collection (blood group) or serial faeces, urine, and tissue sample collection (excretion group). Animals were housed individually.

On day 1 of the study, a 200µl aliquot of the particular dosing solution was applied to a 24 cm^2 area of shaved skin on each of the animals backs. Each application site was covered with 2 layers of cotton gauze and secured

by an adhesive elastic dressing wrapped over the gauze and around the animals abdomen. The wrap was removed from each animal 8 hours after treatment. The application site was then washed thoroughly.

Blood samples were collected and radioassayed at 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours post-treatment. The concentration in the blood following dermal application of 14C-Oxamyl was determined by monitoring the concentration of radioactivity in whole blood samples at the various time intervals. Urine and faeces were collected during the following intervals post-treatment: 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours. Material balance, excretion rate and tissue distribution profile were determined in this group of animals.

II. RESULTS

The objective of this study was to estimate the extent and rate of systemic absorption following dermal exposure to Oxamyl.

One animal assigned to the high dose blood group died and another in the low dose blood group was killed prior to completion of the data collection. Neither deaths could be attributed to treatment effects. No other animal in the blood group exhibited any signs of abnormality or illness.

Blood concentration:

Blood concentrations at all times were generally at, or very close to, the detection limit (0.7-0.8 µg/mL for the high dose and 0.1-0.2 µg/mL for the low dose), excluding the one outlier. In the high dose group, blood concentrations of 14C-Oxamyl equivalents were not detectable for the initial 24 hours or after 72 hours. Maximum concentrations were observed at 36 to 72 hours, and these concentrations were approximately at detectable limits. For the low dose group, blood concentrations of 14C-Oxamyl equivalents were generally not detected for the initial 12 hours.

Excretion collection:

All animals assigned to this group survived the study.

Urinary excretion:

Peak urinary excretions of ^{14}C-Oxamyl equivalents in both dose groups were observed between 6 and 48 hours after application. Total urinary excretion accounted for approx. 2 – 3% or the applied dose. Excretion of ^{14}C-Oxamyl equivalents in the urine appeared to be independent of dose with percent excretion and temporal patterns being similar in both dose groups.

Faecal excretion:

The concentrations of ^{14}C-Oxamyl equivalents excreted in the faeces were very small and were maximal 12 to 96 hours post-treatment. The mean percent of the applied dose recovered in the faeces was < 0.3% for both dose groups.

Tissue concentration:

The concentration of ^{14}C-Oxamyl measured in the tissues was generally below, or only slightly above, the detection limits. Approximately 1 – 2% of the ^{14}C-Oxamyl applied to the skin remained at the application after 168 hours.

Gauze, swabs, and cage wash analysis:

The combined ^{14}C-Oxamyl equivalents in the gauze rinse and gauze digest accounted for approximately 53% and 48% of the high and low applied dose, respectively. The swab washes at 8 hours removed approximately 45% and 43% of the high and low applied dose, respectively. Amounts in the final cage washes were below detectable limits. The gauze and swabs accounted for the greatest percentage recovery of the applied doses totaling approximately 98% and 91% in the high and low dose animals, respectively.

Percentage recovery of applied radioactivity:

The average total recovery of the ^{14}C-Oxamyl for the animals in the high dose group was 103% (80-116%) and for the animals in the low dose group was 98% (92-99%).

III. CONCLUSIONS

Bioavailability of ^{14}C-Oxamyl after dermal application was low and occurs slowly. Urinary excretion was the primary route of elimination of the absorbed material and accounted for 2 – 3% of the applied dose. Faecal excretion accounted for < 0.3% of the applied dose and < 2% of the applied dose was recovered from the collected tissues and the carcass.

The amount of ^{14}C-Oxamyl equivalents in the application site skin varied greatly (0.4 – 5.1% of applied dose) indicating variable penetration into the skin or varying efficiency of the washing process. If bioavailability is limited to systemic absorption (i.e. excluding the residue at the application site skin), a mean of 3.3 and 4.8% of the applied doses was available after high and low dose Oxamyl application, respectively. If the residue at the application site skin is included, then 3.9 and 6.6% of the applied dose was available for the high and low doses, respectively. These latter values are taken for the evaluation.

The limited data available from the blood collection samples (due to the very low levels detected) suggests a very slow rate of absorption with peak concentration occurring long after the applied ^{14}C-Oxamyl had been removed. Excluding the one outlier, the maximum concentrations in blood are in line with the expected dose dependency.

The temporal patterns of urinary and faecal excretion of ^{14}C-Oxamyl equivalents also indicate a slow rate of absorption and elimination. While maximum excretion occurred at 12 to 96 hours (test substance being removed at 8 hours post-application), relatively significant amounts were still being excreted at 120 to 168 hours. The temporal patterns of excretion and the percent of applied dose excreted per collection period were similar in the two doses indicating that excretion rate and route were independent of dose.

The dermal adsorption study AMR 614-86, originally submitted under EU Rev8 Point IIIA 7.3.1 and conducted with test material [1-^{14}C]oxamyl, was conducted under guideline U.S. EPA 85-2 (1982). A review of this study indicates that it partially meets the current guideline (B.44). However, when submitted in conjunction with DuPont-6837, it adequately completes the understanding of dermal adsorption.

RMS comments and conclusion:

The study is considered valid.

B.6.2.2 Comparative dermal absorption, *in vitro* using rat and human skin

Study submitted in the EU Dossier in 2003 and included in the first EU approval review.

B.6.2.2/01

Reference: --	**Report**	Fasano, W.J. (2002); Oxamyl (DPX-D1410) 10GR: *In vitro* dermal kinetics of [1-^{14}C] oxamyl in rat, human, and rabbit skin **DuPont Report No.:** DuPont-6837 **Guidelines:** OECD 428 (draft, 2000) GLP:YES

1. Test material: [1-^{14}C]oxamyl technical
   Lot/Batch #: HOTC 567
   Radiochemical purity: >95%

Deviations: Based on OECD draft test guideline 428, no guideline deviations were identified. However only one concentration was tested, corresponding to the undiluted product.

I. MATERIALS AND METHODS

This study was designed to determine the *in vitro* penetration kinetics and the distribution of [1-^{14}C]-Oxamyl in rat, human and rabbit skin during and following a 6-hour exposure to a single, topical application of Oxamyl (DPX-D1410) 10GR granular formulation. This was applied as an undiluted concentrate at 100 g Oxamyl/kg. The formulated product was applied at a rate of 5 mg/cm^2 and remained in contact with the skin for 6 hours. Following exposure, the skin surface was washed and depletion of skin residues monitored until 18 hours post-exposure. The amount of active substance applied per area of skin was approx. 500 µg/cm^2.

The radiochemical purity of [1-^{14}C]-Oxamyl was > 95%; the non-radiolabelled technical grade Oxamyl had a chemical purity of > 97%.

Rat skin used was from female Crl:CD®(SD)IGS BR rats; human skin was obtained post- mortem from the lateral thigh of donors aged 70-81 years; rabbit skin was obtained from the dorsal surface of adult male New Zealand rabbits aged approximately 5 months. Twelve skin preparation per species were tested. The exposure period was 6 hours for each skin preparation.

Three exposure groups (each one consisting of n=4 skin preparations) were used:

1) 0-hour post-exposure group: skins washed and processed immediately following the 6- hour exposure period to determine initial distribution of the applied dose and establish skin residue levels.

2) 6-hour post-exposure group: skins washed immediately following the 6-hour exposure period, held for 6 hours and then processed to determine the final distribution of the applied dose and skin depletion rate.

3) 18-hour post-exposure group: skins washed immediately following the 6-hour exposure period, held for 18 hours and then processed to determine the final distribution of the applied dose and skin depletion rate.

II. RESULTS

The average penetration rate for [1-^{14}C]-Oxamyl 10GR during and following the 6-hour topical exposure period was low and measurable for rat skin only (≤0.24 µg equivalents/cm^2/hr) (Table 10).

At the end of the 6-hour exposure period, independent of species, >99% of the applied dose was washed from the skin. The skin wash accounted for the majority of the unabsorbed portion of applied dose. Following a 6-hour topical exposure to Oxamyl 10GR, only a small fraction of the applied dose had been absorbed (receptor fluid and skin residues) for rat (0.30%), human (0.02%), and rabbit skin (0.25%) (Table 11).

Table 10 Summary of observed penetration rate data (µg equivalents/cm^2/hr) for Oxamyl 10GR

	Rat	Human	Rabbit
0-6 hr penetration rate[a]	0.23	d	d
0-6 hr post-exposure penetration rate[b]	0.24	d	d
6-18 hr post-exposure penetration rate[c]	d	d	d

[a] Average of 0-6 hour mean data from the 0-, 6-, and 18-hour post-exposure groups
[b] Average of 6-hour post-exposure mean data from the 6-, and 18-hour post-exposure groups
[c] 18-hour post-exposure group data only
[d] A penetration rate could not be determined as samples were below the LOD

Table 11 Summary of recovery data for Oxamyl 10GR (% of applied dose)

	Rat	Human	Rabbit
Total absorbed	0.30	0.02	0.25
Skin wash	99.4	103.2	112.9
Total unabsorbed	99.4	103.2	112.9
Total recovery	99.7	103.0	113.1

[a] Average of mean data from the 0-, 6- and 18-hour post-exposure groups

III. Conclusions

The conclusions from the previous evaluation were:

These data show that dermal exposure to Oxamyl 10GR would result in low or negligible penetration and absorption of the active substance for all three species.

RMS comments and conclusion for this renewal

The *in vitro* dermal kinetics study DuPont-6837, originally submitted under EU Rev8 Point IIA 5.8.2.7 and conducted with test material [1-^{14}C]oxamyl, was conducted under guideline OECD 428 (draft, 2000). However the conclusion drawn in 2003 should be revised and the analysis of the study results should be carried out considering the 2012 EFSA guidance on dermal absorption. The analysis is presented below.

Table 12. Summary of Oxamyl 10GR human *in vitro* dermal absorption data compiled from report DuPont-6837 Tables 4, 6 and 8.

Data expressed as a percent of applied dose

	0 h post-dose[a]		6 h post-dose[b]		18 h post-dose[c]	
	Mean	SD	Mean	SD	Mean	SD
Absorbed dose						
Receptor fluid	NA[d]	NA	NA	NA	NA	NA
Skin	0.02	0.02	0.02	0.02	0.03	0.03
Total absorbed	0.02	0.02	0.02	0.02	0.03	0.03
Unabsorbed dose						
Skin wash	101.8	5.89	104.0	11.3	103.7	8.95
Donor chamber	0.01	NA	0.02	NA	NA	NA
Total unabsorbed	101.8	5.89	104.0	11.3	103.7	8.95
Total recovered	101.8	5.90	104.1	11.3	103.1	7.43

[a,b] n=4
[c] n=3 skin except total recovered (n=4)
[d] NA=data not available as samples were below LOD

Table 13 Summary of Oxamyl 10GR rat *in vitro* dermal absorption data compiled from report DuPont-6837 Tables 4, 6 and 8.

Data expressed as a percent of applied dose

	0 h post-dose[a]		6 h post-dose[b]		18 h post-dose[c]	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Absorbed dose						
Receptor fluid	0.15	0.02	0.88	1.28	0.13	0.02
Skin	0.04	0.03	0.03	0.02	0.01	0.00
Total absorbed	0.11	0.11	0.69	1.15	0.11	0.07
Unabsorbed dose						
Skin wash	103.8	8.28	95.2	6.95	99.2	8.48
Donor chamber	0.01	NA[d]	0.00	NA	NA	NA
Total unabsorbed	103.8	8.28	95.2	6.95	99.2	8.48
Total recovered	103.9	8.37	95.9	8.07	99.3	8.54

[a,b,c] n=4
[d] NA=data not available as samples were below LOD

Table 14 Summary of Oxamyl 10GR Rabbit *in vitro* dermal absorption data compiled from report DuPont-6837 Tables 4, 6 and 8.

Data expressed as a percent of applied dose

	0 h post-dose[a]		6 h post-dose[b]		18 h post-dose[c]	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Absorbed dose						
Receptor fluid	NA[d]	NA	0.19	0.06	0.21	NA
Skin	0.15	0.04	0.15	0.07	0.09	0.05
Total absorbed	0.15	0.04	0.24	0.15	0.36	0.15
Unabsorbed dose						
Skin wash	109.9	24.1	127.5	22.6	101.4	9.47
Donor chamber	NA	NA	NA	NA	NA	NA
Total unabsorbed	109.9	24.1	127.5	22.6	101.4	9.47
Total recovered	110.1	24.1	127.8	22.7	101.5	9.50

[a,b,c] n=4
[d] NA=data not available as samples were below LOD

Total absorbed dose is based on radioactivity in the receptor fluid and remaining in the skin. No tape-stripping was done. Absorption of oxamyl was limited and the great majority of the applied radioactivity was recovered in the skin washes in the three species. Recovery of applied radioactivity was complete; therefore, no correction for recovery is needed.

Human

A correction for high variability is needed as the relative standard deviations were ≥25%. Therefore, to be in compliance with the EFSA guidance on dermal absorption, the estimated total absorbed dose should be the sum of the mean and the standard deviation. The total absorbed amount at the different timepoints indicates that the absorption is rapid and not changed over the post-exposure observation time. On this basis the dermal absorption value is considered equal to 0.04%.

Rat

The total absorbed amount at the different timepoints indicates that the absorption is rapid, with a peak at 6 hours post exposure, which is considered as the worst case. A correction for high variability is needed as the relative standard deviations were ≥25%. Therefore, to be in compliance with the EFSA guidance on dermal absorption, the estimated total absorbed dose should be the sum of the mean and the standard deviation. On this basis the highest value for dermal absorption is 1.84% (measured 6 hrs post expsoure).

Rabbit

The total absorbed amount at the different timepoints indicates that the absorption is rapid, and increased with time up to 18 hours post exposure. A correction for high variability is needed as the relative standard deviations were ≥25%. Therefore, to be in compliance with the EFSA guidance on dermal absorption, the estimated total absorbed dose should be the sum of the mean and the standard deviation. On this basis the dermal absorption value at 18 hours representing the worst case is 0.51%.

The study indicate that the dermal absorption of the undiluted product as assessed by an *in vitro* method is rapid and limited in the three tested species, among which human skin has the lowest potential fo absorption: an order of magnitude lower than rabbit and even more when compared to the rat skin.

B.6.2.3 Summary of dermal absorption

Oxamyl 10GR was the representative formulation supporting Annex I listing of oxamyl in the EU. *In vitro* studies using rat, rabbit, and human epidermal membranes with the Oxamyl 10GR concentrate have been conducted. The average penetration rate for [1-^{14}C]Oxamyl 10GR during and following the 6-hour topical exposure period was low and measurable for rat skin only (≤0.24 µg equivalents/cm^2/hr). At the end of the 6-hour exposure period, independent of species, the great majority of the applied dose was washed from the skin. Indeed, the skin wash accounted for the majority of the unabsorbed portion of applied dose.

Following a 6-hour topical exposure to undiluted Oxamyl 10GR, only a small fraction of the applied dose had been absorbed (receptor fluid and skin residues) for rat (1.84%), human (0.04%), and rabbit skin (0.51%). No information is available on in use concentrations.

An *in vivo* rat study was also reviewed and used as supporting information. Bioavailability of [^{14}C]oxamyl after dermal application was very low and occurs slowly. Urinary excretion was the primary route of elimination of the absorbed material and accounted for 2–3% of the applied dose. Faecal excretion accounted for <0.3% of the applied dose and <2% of the applied dose was recovered from the collected tissues and the carcass. The amount of [^{14}C]oxamyl equivalents in the application site skin varied greatly (0.4–5.1% of applied dose) indicating variable penetration into the skin or varying efficiency of the washing process. When beside the amount absorbed (excreted and present in the tissues), the residue at the application site skin is included in the calculation of the absorbable material, then **3.9 and 6.6%** of the applied dose was available for the high and low doses, respectively (corresponding to the undiluted product and the spray concentration, corresponding roughly to 1:9 dilution). The limited data available from the blood collection samples (due to the very low levels detected) suggest a very slow rate of absorption with peak concentration occurring long after the applied [^{14}C]oxamyl had been removed. Excluding the one outlier, the maximum concentrations in blood are in line with the expected dose dependency. The temporal patterns of urinary and faecal excretion of [^{14}C]oxamyl equivalents also indicate a slow rate of absorption and elimination. While maximum excretion occurred at 12 to 96 hours (test substance being removed at 8 hours post-application), relatively significant amounts were still being excreted at 120 to 168 hours. The temporal patterns of excretion and the percent of applied dose excreted per collection period were similar in the two doses, indicating that excretion rate and route were independent of dose.

The results of these studies are summarised in Table 15.

Table 15. Summary of the dermal absorption data

Study	Sample time	Formulation concentrate		Reference
		% Absorbed	Absorption rate (µg/cm²/h)	
In vitro - rat skin	6 h	1.84	0.24	Fasano, 2002 DuPont-6837
	24 h	0.18	ND[a]	
In vitro - human skin	6 h	0.04	ND[a]	Fasano, 2002 DuPont-6837
	24 h	0.06	ND[a]	
In vitro – rabbit skin	6 h	0.36	ND[a]	Fasano, 2002 DuPont-6837
	24 h	0.51	ND[a]	
In vivo - rat	168 h	3.9	ND[a]	[redacted] *et al.*, 1986 AMR 614-86

[a] A penetration rate could not be determined as samples were below the LOD

During the EPCO Expert Meeting 09 (06-07 July 2004) for oxamyl, the human *in vivo* dermal absorption value for this granular formulation was corrected to be 0.04%: this is the value that has been used for the approval of the a.s. for estimating potential exposure to operators, bystanders, residents, and workers. This value was also verified on the basis of the EFSA 2012 Guidance Document: a correction was made and that resulted in the same absorption values, but only using the *in vitro* data from DuPont-6837. This is considered to be a conservative assessment as no tape stripping was conducted. However, since data on the concentrate[1] are available also for the in vivo situation, a triple pack approach can be used, considering the ratio in vitro in vivo in the rat and applying it to the human in vitro.

In vivo human= $\frac{\textit{in vitro}\ \text{human} \times \textit{in vivo}\ \text{rat}}{\textit{in vitro}\ \text{rat}} = \frac{0.04 \times 3.9}{1.84} = 0.08\%$

The value of **0.08%** is proposed as the absorption value for the risk assessment calculations for the **undiluted product.**

Regarding the dilution, since no information are available on the human skin, but the data obtained in vivo with the rat indicate that a difference exist between the undiluted product and the in use 1:9 dilution, it is proposed to use the pro-rata approach as indicated in the EFSA 2012 Guidance Document. Therefore for the **in use dilution** a value of 0.08 x9 = **0.72% is proposed**.

B.6.3 Available toxicological data relating to co-formulants

Safety data sheets (SDS) for each co-formulant can be found in Document H, and are contained within Oxamyl 10GR EU Renewal Dossier, Document J, Part 3, DuPont-40945 EU. Additional data to that contained on the safety data sheets are not currently available to the applicant.

B.6.4 Exposure data

B.6.4.1 Operator exposure

B.6.4.1.1 Estimation of operator exposure

Usage information pertinent to operator exposure is summarised in Table 12.

[1] In vivo data were obtained with Vydal L, a liquid formulation, However, since it represents a 'worst case' with respect to the GR formulation for the end-point of concern (i.e. dermal absorption) it can be accepted.

Table 126 Summary of critical use patterns (*i.e.*, worst case)

Crop	Application rate (kg a.s./ha)	Spray dilution (L spray/ha)	Application equipment	Number applications
Tobacco: pre-plant soil incorporated to a depth of 10 cm	5.5	Not applicable-product applied as a solid	Tractor-drawn broadcast incorporated	1

The UK POEM and the German model do not contain data for the estimation of operator exposure during application of granular formulations into or onto the soil. In lieu of an appropriate model for estimating potential exposure, an operator exposure study was provided (see DuPont-2311 in Point B.6.4.1.2 below). The study was conducted to determine inhalation and dermal exposure to oxamyl during loading and during in row application of Oxamyl 10GR at a rate of 1 kg a.s./ha while planting potatoes. The study results represent operators wearing long pants, long sleeve shirt, and protective gloves for handling the product. Based on observation of the workers, the highest potential for inhalation exposure to oxamyl was during the task of loading. The highest actual exposure was to the hands during application, which based on observations made during the conduct of the study, likely occurred during adjusting of equipment and/or activities related to planting the crop. The highest individual operator exposure was 0.143 mg/person/day by the dermal route and 0.0132 mg/person/day by the inhalation route. The same individual in the study was found to have the highest exposure by both the dermal and inhalation routes. Dermal exposure was the sum of residue detected on the inner whole-body dosimeter, headband, socks, and hand dosimeter gloves. Inhalation exposure was derived by assuming a breathing rate 20.83 L/min to adjust the measured residue captured by the personal air pump.

For the purposes of assessing risk to operators, a systemic AOEL of 0.01 mg/kg bw/day was established for oxamyl based on the NOAEL of 0.1 mg/kg bw where cholinesterase inhibition and decreased body weight were observed at doses >0.1 mg/kg bw from a rat acute neurotoxicity study. A 10-fold safety factor is proposed based on the observations from human studies that indicate the human LOAEL for cholinesterase inhibition is 0.15 mg/kg bw. A dermal penetration factor of 0.04% was established for the granule formulation based on the result of an *in vitro* study results[2] (see Point B.6.2 in this document). 100% absorption of potentially inhaled active substance was assumed.

Worst case exposure from the exposure study:

((0.143 mg/person/day × 0.0004) + 0.0132 mg/person/day)/60 kg/person = 0.00022 mg/kg/day, or 2.2% of the systemic AOEL.

Worst case estimate based on proposed critical GAP of 5.5 kg a.s./ha is estimated by extrapolating the study results:

5.5 × 2.2% of AOEL = 12% of AOEL

This is a reasonable extrapolation since it is based on a product-specific study. In addition, the vast majority of the systemic dose resulted from inhalation exposure and it is generally accepted that more exposure would be anticipated form opening and transferring the contents of more product containers.

Conclusion

Exposure to Oxamyl 10GR during loading and application does not involve a significant risk to the health of operators, assuming the use of proper work clothing (long pants and long sleeve shirt) and the use of protective gloves when handling the product or contacting contaminated surfaces.

[2] EFSA Scientific Report (2005) 26, 1-78, Conclusion on the peer review of oxamyl

B.6.4.1.2 Measurement of operator exposure

Study submitted in the EU Dossier in 2001 and included in the first EU approval review.

B.6.4.1.2/01

Reference: --	**Report**	Brouwer, D.H., Engel, R., de Cock, J.S. (2000); Field study on exposure to oxamyl during the application of Vydate 10G for soil treatment in potatoes **DuPont Report No.:** DuPont-2311 **Guidelines:** OECD/GD(97)148

1. Test material: Oxamyl 10GR
   Lot/Batch #: D1410-395
   Purity: 100 g a.s./kg

Deviations: Not applicable

Materials and methods:

Exposure to Oxamyl during soil treatment was investigated in the major potato growing area of The Netherlands (De Veenkoloniën) during April and May, 1999. Granules of Vydate 10G (DPX-D1410 10G; batch D1410-395; purity 10.02% Oxamyl a.s.), packaged in 10-kg capacity containers, were applied by broadcast row application using a tractor with cab and granule applicators mounted at the seeder which consisted of two hoppers. Applicators with a delivery rate dependent and independent of driving speed were used. Ten professional and fully licensed applicators participated in the study on 9 different test sites.

Operator inhalation exposure during loading and application combined was monitored using a IOM sampling head consisting of a pump and glass fibre filters with a flow rate of 2 L/min. Dermal exposure during loading and application combined was estimated using whole-body 100% cotton dosimeters including long-sleeved shirt, long-sleeved underpants, coverall, headband and socks. All items were analysed separately for contamination. The shirt, underpants and coveralls were divided into sections and each section analysed separately. Hand contamination was estimated during loading and application separately using 100% cotton gloves. These were worn under Marigold green nitril G 25G gloves during loading only.

Blank samples for inhalation and dermal exposure consisted of sampling filters and cotton dosimeters exposed to similar environmental conditions for a similar time period in the vicinity of the test field. The efficiency of the inhalation and dermal dosimetry techniques was investigated using spiked filters and cotton clothes and the same environmental exposure and analysis regimen.

The amount of test substance applied and the total area treated by each subject was calculated. Environmental conditions were recorded throughout loading and application.

Samples were extracted by sonification and mechanical shaking in 0.01% v/v aqueous acetic acid followed by centrifugation (filters only). The concentration of Oxamyl was determined by reverse-phase HPLC with UV detection. The LOD was set at 4 µg/L and the LOQ was set at 10 µg/L (20 µg/L for socks). Within-day recovery was determined using spiked matrix samples and was ascertained to be ≥97%. Between day recovery, analysed over 10 days, showed that Oxamyl was stable under the conditions of storage up to 8 days. Therefore, field samples were analysed as soon as possible and stored under standard conditions (2 – 10°C). Field fortifications of all dosimeter matrices were prepared to assess losses and cross- contamination during all phases of sample collection, handling, storage and transportation were investigated.

Findings:

Environmental conditions:

Environmental conditions during the sampling period differed from day to day warranting postponement of the application on several occasions. However, no application was interrupted even when light rainfall occurred.

Application:

The treatment area was 4.61 ±0.88 ha (mean ±SD). The calculated application rate (observed) was 10.4 ±1.3 kg/ha (mean ±SD).

Table 137 Details of Vydate 10G application over 1 day

Test subject	Treated area (ha)	Product loaded (kg)	Product applied (kg)*	Accepted application rate (kg/ha)	Observed application rate (kg/ha)
1	4.4	50.0	49.5	9.3	11.2
2	3.8	50.0	45.7	10.6	12.0
3	4.0	44.3	41.0	8.5	10.2
4	6.9	60.0	55.4	10.5	8.0
5	4.3	50.0	42.0	10.5	9.8
6	4.4	50.0	44.2	8.5	10.0
7	4.2	43.7	40.9	8.8	9.6
8	4.3	56.1	53.4	8.7	12.4
9	5.0	50.0	49.5	11.1	9.9
10	4.8	51.6	50.0	8.6	10.4
Mean±SD	**4.6** ± **0.9**	**50.6** ± **4.8**	**47.2** ± **5.2**	**9.5** ± **1.0**	**10.4** ± **1.3**

***** The difference between the product loaded and applied is the residue remaining on the hopper.

Inhalation exposure:

Details of the operator inhalation exposure are shown in

Table 14. The high TWA and exposure readings for subject 8 were explained by an excessive number of granule spills perpetrated by this individual during loading.

Table 148 Inhalation exposure to Oxamyl

Test subject	Duration (min) [1]	TWA[2] (μg/m^3)	Exposure[3] (μg)	Exposure/ kg Oxamyl[4] (μg/kg)
1	401	0.314	2.62	0.524
2	317	0.138	0.91	0.182
3	299	0.580	3.61	0.814
4	353	0.448	3.30	0.548
5	224	0.482	2.25	0.449
6	347	0.402	2.90	0.579
7	405	0.447	3.77	0.862
8	320	1.980	13.20	2.350
9	310	0.243	1.57	0.313
10	285	1.280	7.60	1.470
Mean	**326**	**0.631**	**4.17**	**0.809**

[1] Duration of inhalation sampling
[2] Time weighted average concentration (μg/m^3) of Oxamyl in the breathing zone during the sampling period
[3] Exposure (μg of Oxamyl) calculated from TWA (μg/m^3) x ventilation rate (20.83 L/min) x duration of sampling (min)
[4] Exposure (μg of Oxamyl) per kg Oxamyl loaded (Vydate 10G loaded x 0.102)

Dermal exposure:

Of the 120 dosimeter samples analysed for contamination, 70 gave readings ≥the LOQ. The front torso section of the coverall showed the highest contamination. Very high dosimetry readings were obtained from subject 8 which corroborates with the high inhalation and dermal exposures recorded in this individual. Only 5 of the 60 samples for actual exposure (dosimeters closest to the skin) gave readings > the LOQ. Out of 35 dosimetry gloves used during loading, 1 contained a quantifiable amount of Oxamyl while 15 out of 38 dosimetry gloves used during application showed quantifiable residues. Subject 8 picked up spilled potatoes from the location where Vydate 10G granules were loaded and spilled on the ground.

Table 15 Dermal exposure to Oxamyl (μg) from whole-body dosimetry including hands

Subject	Potential dermal exposure				Actual dermal exposure			
	Coverall	**Headband**	**Socks**	Total	Inner[1]	Hands		Total
						Loading[2]	application	
1	142.5	0.1	1.0	143.6	7.6	3.0	4.7	15.3
2	85.9	2.5	5.0	93.4	3.2	2.0	18.0	23.2
3	98.6	6.9	0.5	**106.0**	18.3	1.5	40.6	60.4
4	71.2	1.3	2.5	**75.0**	3.0	1.5	22.7	27.2
5	29.5	0.5	0.5	**30.5**	3.2	1.5	9.2	13.9
6	91.0	4.5	2.5	**98.0**	5.6	3.5	12.3	21.4
7	50.1	1.1	1.0	**52.2**	4.8	10.0	32.3	47.1
8	699.9	38.0	5.0	**742.9**	14.5	2.5	83.0	100.0
9	96.8	1.6	5.0	**103.4**	20.1	1.5	9.9	31.5
10	144.4	4.3	0.5	**149.2**	14.6	2.0	9.9	26.5
Mean	**151.0**	**6.1**	**2.4**	**159.4**	**9.5**	**2.9**	**24.3**	**36.7**

[1] Inner exposure (μg of Oxamyl) from long-sleeved shirt and long-sleeved underpants dosimeters closest to the skin
[2] Dosimetry gloves were worn beneath protective nitril gloves during loading only

Table 16 Dermal exposure to Oxamyl from whole-body dosimetry including hands expressed as μg of Oxamyl per kg Oxamyl handled

Subject	Potential dermal exposure				Actual dermal exposure			
	Coverall	**Headband**	**Socks**	Total	Inner[1]	Hands		Total
						loading	application	
1	28.50	0.02	0.20	28.72	1.52	0.60	0.94	3.06
2	17.18	0.50	1.00	18.68	0.64	0.40	3.60	4.64
3	22.26	1.56	0.11	23.93	4.13	0.34	9.16	13.63
4	11.87	0.22	0.42	12.50	0.50	0.25	3.78	4.53
5	5.90	0.10	0.10	6.10	0.64	0.30	1.84	2.78
6	18.20	0.90	0.50	19.60	1.12	0.70	2.46	4.28

Subject	Potential dermal exposure				Actual dermal exposure			
	Coverall	**Headband**	**Socks**	Total	Inner[1]	Hands		Total
						loading	application	
7	11.46	0.25	0.23	11.95	1.10	2.29	7.39	10.78
8	124.76	6.77	0.89	132.42	2.58	0.45	14.80	17.83
9	19.36	0.31	1.00	20.68	4.02	0.30	1.98	6.30
10	27.98	0.83	0.10	28.91	2.83	0.39	1.92	5.14
Mean± SD	**28.75**	**1.15**	**0.46**	**30.35**	**1.91**	**0.60**	**4.79**	**7.30**
75th percentile	**26.55**	**0.88**	**0.79**	**27.52**	**2.77**	**0.56**	**6.49**	**9.66**

[1] Inner exposure (µg of Oxamyl) from long-sleeved shirt and long-sleeved underpants dosimeters closest to the skin

Field blanks and field spikes:

No systematic cross-contamination occurred during the sampling and analytical procedures. The results of field spike analysis indicated that Oxamyl residue trapped by the sampling matrices during loading and application was stable.

Potential / actual operator exposure:

Dermal absorption of Oxamyl was calculated for human, rat and rabbit skin in vitro with both 10SL and 10GR formulations and for rat skin in vivo with 10SL, Vydate L and Spray formulations. The in vivo and in vitro studies using the Oxamyl 10SL formulation used the same exposure regimen (6 hours) and the same application rate (1mg/cm2). Using the mass balance equation and the worst-case absorption value from the in vivo study (inclusive of residue remaining at the application site), the in vivo dermal absorption of Oxamyl in the 10SL formulation in humans is 1.82% of the applied dose. Therefore, the potential and actual systemically absorbed Oxamyl dose is 3.57 and 0.67 µg/day, respectively. Assuming 100% of the inhaled residue is absorbed this gives an actual systemic exposure of 4.84 µg and an overall potential exposure of 7.74 µg. Based on an operator body weight of 60 kg, these values correspond to 0.081 and 0.129 µg/kg bw/day, respectively 47- to 74-fold lower than the systemic AOEL.

Based on the absorption estimate for human skin in vitro using the 10GR formulation (0.02% of the dose), the proportion of the Vydate 10G contamination that could be systemically absorbed is 0.039 µg for potentially absorbed residue and 0.007 µg for actually absorbed residue. Assuming 100% of the inhaled residue is absorbed this gives an actual systemic exposure of 4.177 µg/day and an overall potential exposure of 4.209 µg/day. Based on an operator body weight of 60 kg, these values correspond to 0.070 µg/kg bw/day in both cases or 86-fold lower than the systemic AOEL.

Conclusion:

Actual body and hand exposure to Oxamyl during loading was negligible, the majority of samples containing no detectable amount of Oxamyl. Average inhalation exposures during loading and application were also low. Excessive dermal and inhalation exposures were associated with human error during loading. All but one subject had the rear window of the tractor cab open during application. These results suggest that dermal and inhalation exposures are chiefly experienced during the loading procedure. The high contamination of dosimetry gloves during application most likely resulted from direct contact with contaminated surfaces such as the cab, seeder or granule hopper.

The measurement of operator exposure study DuPont-2311, originally submitted under EU Rev8 Point IIIA 7.2.1.2 and conducted with test material Oxamyl 10GR, was conducted under guideline OECD/GD(97)148. A review of this study indicates that it was conducted under and fully meets the current guideline.

RMS comments and conclusion:

A justification to use 1ha for the surface of area treated in one day should be provided.

B.6.4.2 Bystander and resident exposure

The very low vapour pressure and high water solubility of oxamyl and its direct incorporation into soil at the time of application preclude significant vapour concentration. No inhalation or dermal exposure to bystanders and residents is anticipated.

B.6.4.2.1 Estimation of bystander and resident exposure

Due to the physical/chemical properties of oxamyl and the nature of the application technique exposure to bystanders and residents is anticipated to be negligible.

B.6.4.2.2 Measurement of bystander and resident exposure

Due to negligible anticipated exposure to potential bystanders/residents, no measurement of exposure was done.

B.6.4.3 Worker exposure

Since Oxamyl 10GR is applied directly to soil at planting time and there is negligible likelihood of worker exposure by contact with crop foliage, estimating exposure based on soil residue rather than foliar residue is presented here.

B.6.4.3.1 Estimation of worker exposure

Estimation of worker exposure assuming personal protective equipment is not used

A conservative exposure estimate can be made using the approach in the EUROPOEM II report.[3] Potential dermal exposure (PDE) can be calculated as follows:

$$PDE = C \times DA \times SA \times T$$

Where:

C = concentration of active substance in soil (0.0055 mg/cm³)
DA = adherence of soil to skin (0.00029 cm³/cm²)
SA = exposed skin surface area (820 cm²)
T = percent of soil residue transferred to skin (100%)

The value for C is based on the maximum broadcast application rate of 5500 g of oxamyl/ha (55 kg of 100 g a.s./kg formulated product) and assuming it is uniformly distributed in the soil to a depth of 10 cm. This is the worst-case soil concentration, equivalent to 5.5 g a.s./m³ or 0.0055 mg a.s./cm³. DA is based on the EUROPOEM cited value of 0.44 mg soil/cm² of skin surface area and an assumed soil bulk density of 1.5 g/cm³. SA is based on the surface area of the hands assumed to be 820 cm². T is assumed to be 100% as a conservative figure.

$$PDE = 0.0055 \text{ mg/cm}^3 \times 0.00029 \text{ cm}^3/\text{cm}^2/\text{day} \times 820 \text{ cm}^2 \times 1 = 0.0013 \text{ mg a.s./day}$$

Assuming 60 kg body weight and 0.04% dermal absorption gives a systemic dose equivalent to <1% of the AOEL of 0.01 mg/kg/day.

This is a conservative assessment, since residue transfer to skin is assumed to be 100%. In addition, oxamyl degrades in soil, and the application is made at planting time when no re-entry work is likely to occur for some time.

3 EUROPOEM II (2002) Report of the Re-Entry Working Group – Post-Application Exposure of Workers to Pesticides in Agriculture. EUROPOEM II Project FAIR3-CT96-1406, December, 2002.

Conclusion

The risk assessment detailed above indicates that it is unlikely that exposures to Oxamyl 10GR through agricultural use will result in exceedance of the AOEL for oxamyl.

B.6.4.3.2 Measurement of worker exposure

The risk assessment detailed above (Point B.6.4.3.1) indicates that exposures to Oxamyl 10GR through agricultural use represent an acceptable level of risk to field workers. Therefore, no actual measurement of exposure was done.

B.6.5 Exposure and risk assessment

Please refer to section B.6.4

B.6.6 References relied on

List of information, tests and studies which are considered as relied upon by the RMS for the evaluation with a view to the approval of the active substance.

Sorted by Annex Point

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
B.6.1.1/01	[redacted]	1999	Oxamyl 10G: Acute oral toxicity study in rats. [redacted] DuPont-2703 GLP: Yes	Y	DuPont
B.6.1.2/01	[redacted]	1999	Oxamyl 10G: Acute dermal toxicity in rats. [redacted] DuPont-2810 GLP: Yes Published: No	Y	DuPont
B.6.1.3/01	[redacted]	1999	Oxamyl 10G: Inhalation median lethal concentration (LC_{50}) in rats. [redacted] DuPont-1987 GLP: Yes Published: No	Y	DuPont
B.6.1.4/01	[redacted]	1999	Oxamyl 10G: Primary dermal irritation study in rabbits. [redacted] DuPont-2453 GLP: Yes Published: No	Y	DuPont

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
B.6.1.5/01	[redacted]	1999	Oxamyl 10G: Primary eye irritation study in rabbits. [redacted] DuPont-2640 GLP: Yes Published: No	Y	DuPont
B.6.1.6/01	[redacted]	1999	Oxamyl 10G: Evaluation of the potential dermal sensitization in the Guinea pig (modified Buehler method). [redacted] DuPont-1953 GLP: Yes Published: No	Y	DuPont
B.6.2.1/01	[redacted]	1986	Dermal absorption of [^{14}C]-oxamyl in the rat. [redacted] AMR 614-86 GLP: Yes Published: No	Y	DuPont
B.6.2.2/01	Fasano, W.J.	2002b	Oxamyl (DPX-D1410) 10GR: *In vitro* dermal kinetics of [1-14C] oxamyl in rat, human, and rabbit skin. DuPont Haskell Laboratory DuPont-6837 GLP: Yes Published: No	Y	DuPont

Annex No., Reference No.	**Author(s)**	**Year**	**Title Source Company Report No. GLP or GEP Status (where relevant) Published or not**	**EU Data Protection Claimed (Y/N)**	**Owner**
B.6.4.1/01	Brouwer, D.H., Engel, R., de Cock, J.S.	2000	Field study on exposure to oxamyl during the application of Vydate 10G for soil treatment in potatoes. TNO Nutrition & Food Research DuPont-2311 GLP: Yes Published: No	N	DuPont

Sorted by Author

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
B.6.4.1/01	Brouwer, D.H., Engel, R., de Cock, J.S.	2000	Field study on exposure to oxamyl during the application of Vydate 10G for soil treatment in potatoes. TNO Nutrition & Food Research DuPont-2311 GLP: Yes Published: No	N	DuPont
B.6.2.2/01	Fasano, W.J.	2002b	Oxamyl (DPX-D1410) 10GR: *In vitro* dermal kinetics of [1-14C] oxamyl in rat, human, and rabbit skin. DuPont Haskell Laboratory DuPont-6837 GLP: Yes Published: No	Y	DuPont
B.6.1.1/01	[redacted]	1999	Oxamyl 10G: Acute oral toxicity study in rats. [redacted] DuPont-2703 GLP: Yes	Y	DuPont
B.6.1.2/01	[redacted]	1999	Oxamyl 10G: Acute dermal toxicity in rats. [redacted] DuPont-2810 GLP: Yes Published: No	Y	DuPont

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
B.6.1.4/01	[redacted]	1999	Oxamyl 10G: Primary dermal irritation study in rabbits. [redacted] DuPont-2453 GLP: Yes Published: No	Y	DuPont
B.6.1.5/01	[redacted]	1999	Oxamyl 10G: Primary eye irritation study in rabbits. [redacted] DuPont-2640 GLP: Yes Published: No	Y	DuPont
B.6.1.6/01	[redacted]	1999	Oxamyl 10G: Evaluation of the potential dermal sensitization in the Guinea pig (modified Buehler method). [redacted] DuPont-1953 GLP: Yes Published: No	Y	DuPont
B.6.2.1/01	[redacted]	1986	Dermal absorption of [^{14}C]-oxamyl in the rat. [redacted] AMR 614-86 GLP: Yes Published: No	Y	DuPont

Annex No., Reference No.	**Author(s)**	**Year**	**Title Source Company Report No. GLP or GEP Status (where relevant) Published or not**	**EU Data Protection Claimed (Y/N)**	**Owner**
B.6.1.3/01	[redacted]	1999	Oxamyl 10G: Inhalation median lethal concentration (LC_{50}) in rats. [redacted] DuPont-1987 GLP: Yes Published: No	Y	DuPont