(2)

Data Evaluation Report

Chemical Oxadiazin

Study Type Dermal absorption (GL 85-3)

Citation
Dermal absorption of [Oxadiazin-4-^{14}C] CGA 293343 Formulated as WG 25 (A-9584C) in the Rat. S. Hassler. Novartis Crop Protection AG. Study No 027AM07. Novartis Nexus Number 970-98. Sept 10, 1998. MRID 447034-03

Reviewed by Robert P. Zendzian PhD
Senior Pharmacologist

Core Classification Unacceptable (cannot be upgraded)

Summary
The study, in male rats(four per dose exposure), utilized three doses 2.5, 25 and 242 ug/cm^2. Exposure durations were as follows; 6 hours, 6 hour wash - 24 hour total exposure and 6 hour wash - 48 hour total exposure. The application site was not washed prior to exposure. A wash 24 hours prior to dosing is required in order to standardize the condition of the application site. The exposure durations tested do not fit even the minimum requirements in the guideline and are of no value for risk assessment. For a full study exposure durations are 0.5, 1, 2, 4, 10 and 24 hours. For the minimum study exposure durations are 1, 10 and 24 hours. Other exposure scenarios, including wash off, may be used if a risk assessment indicates unacceptable risk at specific exposure scenarios which may be modified by the results of a dermal absorption study.

Further the data generated in the study do not follow the expected dose and duration of exposure relationships for a chemical with the physical properties of Oxadiazin. The percent absorbed does not increase consistently with increasing exposure duration despite a significant portion of the dose remaining on the skin at termination. The percent absorbed does not decrease consistently with increasing dose as an indication of saturation. Because of the minimal data generated it is not possible to determine the cause of this variation.

From the table on page 30 of the report (attached).

	Absorbed		
	2.5	25	242 ug/cm^2
6hrs	0.44	2.72	0.71
24hrs*	1.52	1.63	0.59
48hrs*	1.31	2.87	0.76

	Treated Skin		
	2.5	25	242 ug/cm^2
6hrs	19.95	24.33	4.56
24hrs*	19.76	20.67	3.96
48hrs*	18.31	20.92	3.76

*6 hour wash

PMRA ARLA

Primary Reviewer: P. Maloney/C. Norman **Date:** June 28, 1999
Secondary Reviewer: _____ **Date:** _____

STUDY TITLE: Dermal Absorption of [Oxadiazin-4-^{14}C] CGA 293343 (Thiamethoxam) Formulated as WG 25 (a-9584C) in the Rat

STUDY TYPE: Rat *in vivo* Dermal Absorption

TEST MATERIAL:

Company Code: CGA 293343
Chemical name:
IUPAC: 3-(2-Chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene-N-nitroamine
CA: 3-[2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-4H-1,3,5-oxadiazin-4-imine
CAS #: 153719-23-4
Chemical Formula: $C_8H_{10}ClN_5O_3S$

SYNONYMS: Thiamethoxam technical

CITATION: Hassler, S. Dermal Absorption of [Oxadiazin-4-^{14}C] CGA 293343 Formulated as WG 25 (a-9584C) in the Rat. NOVARTIS Crop Protection AG, Basel, Switzerland. Study 027AM07 September 10, 1998.

Hassler, S. Dermal Absorption of [Oxadiazin-4-^{14}C] CGA 293343 Formulated as WG 25 (a-9584C) in the Rat. Individual Data. NOVARTIS Crop Protection AG, Basel, Switzerland. Study 027AM07 September 10, 1998. MRID 44703403.

SPONSOR: Novartis Crop Protection AG, CH-4002 Basel, Switzerland. Product Unit Insecticides. (Represented by B. Duverger)

EXECUTIVE SUMMARY:

Groups of 12 rats (Tif:RAIf(SPF)) were administered thiamethoxam as a dispersible granular formulation at each of three dose levels: 2.5, 25.3, and 242 µg ai/cm^2. The application site was subject to a wash after 6 hr. Groups of 4 animals at each dose level were sacrificed after 6, 24, or 48 hours. Urine and feces were collected at 0-6 hr, 6-24 hr, and 24-48 hr intervals. Blood samples were taken at 0.5, 1,2,4,6,8,24,48 hrs, and whole blood and plasma were collected from each animal after sacrifice. Skin wash, the application apparatus (0-ring + permeable tape), treated skin site, residual carcass, and untreated skin were also collected for analysis. Neither expired air or individual tissues were collected for analysis.

Mean total recovery of radioactivity ranged from 95.11 to 99.74% of the applied dose. The majority of radioactivity was

recovery from the skin wash. Mean radioactivity in the skin test site ranged from 3.76 to 24.33%; in urine from 0.13 to 2.61%; and in the feces from 'not detectable' to 0.14%. Mean radioactivity in whole blood did not exceed 0.02% and in the carcass did not exceed 0.72%. Estimates of dermal absorption were based on the sum of radioactivity in skin test site, urine, feces, blood, and carcass. After 6 hr, dermal absorption was 20.39%, 27.05 and 5.27% at the low, middle and high dose respectively. After 24 hr, dermal absorption was 21.28, 22.30 and 4.55% at the low, middle and high dose respectively. After 48 hr, dermal absorption was 19.62, 23.79 4.52% at the low, middle and high dose respectively.

Percentage (%) Dermal Absorption: 27.0 (rounded off from 27.05, highest mean dermal absorption value across all groups). This value is considered to represent the potential cumulative dermal absorption of test material that might occur after a 10 hour dermal exposure. See comments below.

Comments about Dermal Absorption: As the study design (i.e., longest collection period was 48 hr) did not permit analysis of the fate of skin bound residues, residues at skin site were included in determination of dermal absorption.

Given the uncertainty regarding actual deposition ($\mu g/cm^2$) of thiamethoxam under field conditions, and the differences in the test formulation and the proposed end-use formulation (i.e., formulation type, active ingredient composition, formulant composition differences) it was considered appropriate to use a conservative estimate of dermal absorption (i.e., 27%).

GUIDELINE OR PROTOCOL FOLLOWED: This study was conducted according to the draft OECD Guideline for Testing of Chemicals, Percutaneous Absorption: *in vivo* Method document, June 1996.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material:

Company Code: CGA 293343
Chemical name:

IUPAC:	3-(2-Chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene-N-nitroamine
CA:	3-[2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-4H-1,3,5-oxadiazin-4-imine
Common name:	Thiamethoxam technical
Lot/Batch #:	Radiolabelled test substance: ILS-194.1
	Non-radiolabeled test substance: AMS 780/102
Purity:	Radiolabelled test substance: 99.8%
	Non-radiolabeled test substance: 99.3%
CAS #:	153719-23-4
Structure:	$C_8H_{10}ClN_5O_3S$
Radiolabelling:	[Oxadiazin-4-^{14}C] CGA 293343
Specific Activity :	1940 kBq/mg = 52 µCi/mg

2. Relevance of Test Material to Proposed Formulation(s):

The test formulation, formulated as a water dispersible granular, had the following composition:

Active ingredient:	CGA 293343 (thiamethoxam technical)	25.0% w/w
Formulants:	sodium lignosulfonate	5.0 % w/w
	sodium lauryl sulfate	3.75% w/w
	butylated polyvinylpyrrolidone	1.25% w/w
	kieselguhr	5.0% w/w
	cornstarch	60.0% w/w

The proposed end-use formulation, HELIX, would be formulated as a water-based flowable suspension. The composition of HELIX is provided in Appendix 1.

The test formulation is significantly different from the proposed end-use formulation, HELIX. The test formulation is a water dispersible granular formulation, while HELIX is a water-based flowable suspension. In addition, HELIX contains 3 additional active ingredients, and a different formulant composition that the test formulation. Key differences are outlined below:

Parameter	Test Formulation	HELIX
Concentration of Thiamethoxam	25%	20.7%
Concentration of other Active Ingredients	n/a	1.77%
Concentration of formulants (except diluent)	15%	[redacted]
Diluent	60% corn starch	[redacted]

To address these formulation differences, the applicant (correspondence to S. Muir, PMRA from P. Chan dated January 18, 1999) noted the following considerations:

- the vehicle for the test formulation was water, which is appropriate for evaluating dermal absorption of the water-based HELIX formulation.
- the low concentration of other active ingredients is not anticipated to influence dermal absorption of thiamethoxam
- formulant differences are not considered significant, as the vehicle (i.e. water) is the primary component of the dose
- use of a 10-fold uncertainty factor would accommodate any formulation differences.

It was concluded that the formulation differences are a study limitation.

3. Test animals:

Species: Rats
Strain: Tif: RAI f (SPF)
Gender: male
Age/weight: approximately 8 weeks old, approx. 250 g at study initiation
Source: Biological Research Laboratories (BRL), Fullinsdorf, Switzerland
Housing: Rats were kept individually in plexiglass metabolism cages.
Diet: Animals were allowed free access to the certified standard diet.
Water: Tap water was offered ad libitum at all times.
Temperature: animals were kept in rooms maintained at 21± 1°C
Humidity: 48-78%
Air Exchange: not reported
Photo period: 12 hour light/dark cycles
Acclimatization: rats were kept in groups for five days to acclimatize to the laboratory environment, and separated for one day in the metabolism cage with a shaved dorsal area before treatment.

B. METHODS

1. Dose

Rationale: Although not specified in the report, the middle dose appears to be selected to represent a typical concentration recommended for use in the field (i.e. 50 g ai/200L applied to 1 ha). Agricultural uses of thiamethoxam are not currently

proposed for use in Canada. The end-use formulation proposed for Canadian use is a seed treatment use. The worker exposure assessment for HELIX should be consulted to determine whether the dose levels in this study are representative of worker exposure during seed treatment.

Actual Doses: 2.5, 25.3, and 242 µg ai/cm^2 . These values represent the mean of three control doses conducted for each dose level.

Dose volume: 100 µL

2. Dose Preparation

Preparation: The blank formulation consisted of all formulants minus the active ingredient. Stock solutions were prepared by mixing the blank formulation with [Oxadiazin-4-^{14}C]-labelled CGA 293343 (thiamethoxam technical). The radiolabel had a specific activity of 1940 kBq/mg (52 µCi/mg) For the high dose group only, radiolabelled formulation was diluted with non-radiolabelled. The formulations were prepared separately for all dose groups.

To prepare the stock solutions, [Oxadiazin-4-^{14}C]-labelled thiamethoxam was dissolved in a mixture of dichloromethane/methanol/dimethyl sulfide 49/49/2 (v/v/v), and the concentration of radioactivity determined by LSC. An appropriate volume of the radiolabelled stock solution was then added to the blank formulation to create the dose. After homogenisation, the solvents were removed by evaporation. Prior to application, the formulated test substance was mixed with water, and the resulting suspension was sonicated and stirred to create a homogeneous suspension. The volumes of stock solution and blank formulation utilized for the three dose levels are outlined in Table 1:

Table 1 Dose Preparation

Dose Group	Stock Solution	Water Volume (µL)	Mean Actual Applied Dose	
			kBq/ animal	µg/cm^2 [2]
Low	0.17 mL = 0.74 mg ai	3000 µL	48	2.5
Middle	1.7 mL=7.4 mg ai	3000 µL	490	25.3
High	2.7 mL = 11.7 mg ai	3000 µL	734	242

[2] Application was made to 10 cm^2

No information was given regarding the storage period of prepared dose suspensions before application.

3. Number of animals/group: Twelve rats were dosed at each of 3 dose levels. Groups of 4 animals per dose level were sacrificed at 6, 24 or 48 hr.

4. Application Site Preparation: The day before dosing, a dorsal area of 25 - 35 cm^2 was shaved with electric clippers, taking care not to abrade the skin. The study report did not state whether the shaved area was washed prior to exposure. Prior to dosing, a double O-ring (two rings glued onto each other) was glued to the shaved skin using cyanoacrylate adhesive. The inside area of the ring was approximately 10 cm^2.

5. Application Procedure:

Application of Dose: The 100 µL dose was applied to the skin inside the O-ring and spread evenly across the surface of the skin site using a syringe. The dosing site was then covered with permeable tape. Each rat was then fitted with a collar to prevent ingestion of the test material. During dosing and washing, rats were anaesthetized with isoflurane.

Washing Procedure: At 6 hr, the permeable tape cover was removed and saved for analysis. The study report states that the application site was washed "at least" 3 times with a mild soap solution (pH 5.0). Washes was conducted using cotton swabs. After washing, the skin was dried using cotton swabs, and a fresh cover tape was applied to the O-ring. All cotton swabs used for the skin wash were rinsed with 50 mL methanol. Washing was done without removal of the O-ring apparatus.

5. Sample Collection and Preparation:

Termination periods: Groups of 4 animals per dose level were sacrificed at 6 hr, immediately after the skin wash;
Groups of 4 animals per dose level were sacrificed at 24 hr;
Groups of 4 animals per dose level were sacrificed at 48 hr.

Method of sacrifice: Animals were sacrificed by overdose of carbon dioxide in a desiccator.

Urine and feces: Urine and feces were collected over the 0-6 hr interval for all groups; as well as the 6-24 hr time interval for rats sacrificed at 24 and 48 hr, and the 24-48 hr interval for rats sacrificed at 48 hr.

Urine collection containers were surrounded by solid carbon dioxide at all times. Except for transfer into the storage vessels, the urine specimens were kept frozen. Feces were collected at ambient temperature, however, after collection, the specimens were kept frozen. The study report did not detail the duration of storage of urine and feces. No mention is made in the study report of whether residual urine was collected from the bladder after sacrifice.

Blood: Samples were taken at multiple intervals from animals terminated after 48 hr only. Samples were taken at the following intervals: 0.5, 1,2,4,6,8,24,48 hours. Blood samples were taken from the tail vein by cutting the tip of the tail. These samples were analyzed immediately after collection. Terminal whole blood and plasma samples were collected from all animals after sacrifice. This terminal blood was collected into heparinized tubes, and plasma was separated by centrifugation. Whole blood samples were analyzed immediately, and plasma was kept frozen until analysis. No details were given on the method of whole blood sampling at sacrifice, and no information was given regarding the storage time for plasma samples.

Cover tapes and O-ring: After sacrifice, cover tapes and the O-ring were combined in one sample, and extracted two times with approx. 80 mL methanol. No details were given on how the O-ring was removed.

Application site skin: After sacrifice, the skin at the application site was removed and saved for analysis. These samples were kept at ambient temperature until analysis. The study report does not indicate how long samples were stored before analysis. A small piece of non-treated skin was also excised from the shaved area away from the application site. The study report does not give the size of the non-treated skin sample.

Residual carcass: The residual carcasses were retained and kept frozen.

Cage wash: After the collection period, cages were rinsed with a water/ethanol (1:1 v/v) solution. Cage wash was kept at ambient temperature until analysis.

Skin wash: Skin wash rinsate was collected.

Note: expired air was not collected during this study, and individual organs and other tissues were not analysed separately from the carcass. No mention was made of residual urine collection from the bladder after sacrifice.

Sample preparation methods are summarized in Table 2.

Table 2. Sample Preparation

Sample Media	Preparation Details
Diluted dose solution Urine Cage wash Skin wash O-ring and cover extract, Plasma	Aliquots were added directly to the scintillation mixture (Irga-Safe plus[10]) for analysis.
Faeces Carcass Blood	For fecal samples, water was added, and the sample was homogenized with a pestle. Radioactivity was determined after combustion. Similarly, aliquots of the residual carcass were combusted after homogenization with a commercial chopper. Feces, carcass and blood samples were combusted using a Packard Sample Oxidizer System 387[14]. The $^{14}CO_2$ produced from combustion was then absorbed in Carbosorb[14] and mixed with scintillation fluid (Permafluor E+[14]) prior to counting.
Skin	The radioactivity in treated and untreated skin was determined after digestion in Soluene0350[14] tissue solubilizer. The digested samples were neutralized with hydrochloric acid, and mixed with Irgasafe plus[14] before counting.

6. Analysis

Radioanalysis: Radioactivity was measured using Liquid Scintillation Counting on Packard Tri-Carb scintillation counters (model 2000CA) equipped to compute quench-corrected dpm. Background values were measured for each sample run using the respective scintillation mixture with no sample. For measurement of radioactivity in liquid samples, aliquots were added directly to the scintillation mixture (Irga-Safe plus) for analysis. For other samples, samples were prepared as described in Table 2. For samples combusted, the $^{14}CO_2$ produced from combustion was then absorbed in Carbosorb and mixed with scintillation fluid (Permafluor E+) prior to counting.

Validation of radioanalysis procedures was conducted by combusting standards of SPEC-CHEC™-^{14}C (a blend of n-amyl alcohol, 1,3-butanediol, and ^{14}C-stearic acid) at the beginning of each day, and with each sequence of 20 samples. The study report stated that all recoveries were >95%, however, no raw data was given to support these results.
Limits of quantification ranged from 0.0003 to 0.032 µg/g depending on the matrix and dose level.

Thin Layer Chromatography (TLC): Radioactivity patterns and zones were detected and quantified on thin layer plates using a Packard Instant Imager and related software. In addition, a Bio-Imaging Analyser, model BAS 2000 with TINA software was used as an alternative method to read and quantify the radioactive zones. TLC analysis was used with acetonitrile/water/formic acid (90/5/5 v/v/v) or methylethylketone/methanol (80/20 v/v) solvents to test the purity and stability of the test substance and the skin wash. The study results stated that the formulated test substance was found to be stable at the time of application and remained stable on the skin during the 6 hour exposure period. Analysis of the formulated test substance and the skin wash showed that >95% of the radioactivity was found as unchanged thiamethoxam at the time of application, and after the 6 hour exposure period. Limits of Quantification were not provided for this method.

II. RESULTS

1. Signs and Symptoms of Toxicity

All animals showed symptoms of stress, e.g., chromodacyorrhoea, during the first hours after dose administration. A slight

weight loss during the study is also attributed to stress and discomfort. No compound-related effects were reported.

2. Dermal Absorption

Results of analysis are shown in Tables 3a, 3b, and 3c. Recovery of the applied dose was acceptable (i.e., group means ranged from 95.11 to 99.74%). Values at the Limit of Quantification were not included in the calculations as these trace levels would not alter the final results appreciably.

Following dermal administration, the majority of the administered dose was recovered from the skin wash. In all cases, some of the applied dose was retained at the application site (i.e., group means ranged from 3.76 to 24.33%). As the study design did not permit analysis of the fate of residues retain at the application site, dermal absorption was calculated by summing thiamethoxam residues in urine, feces, blood, carcass, cage wash and application site. This value was normalized for the application dose and presented as a % of applied dose.

After 6 hr, dermal absorption was 20.39%, 27.05 and 5.27% at the low, middle and high dose respectively. After 24 hr, dermal absorption was 21.28, 22.30 and 4.55% at the low, middle and high dose respectively. After 48 hr, dermal absorption was 19.62, 23.79 4.52% at the low, middle and high dose respectively.

Given the uncertainty regarding actual deposition ($\mu g/cm^2$) of thiamethoxam under field conditions, and the differences in the test formulation versus the proposed end-use formulation it was considered appropriate to use a conservative estimate of dermal absorption (i.e., dermal absorption of 27%, highest mean dermal absorption value across all groups).

III. DISCUSSION

A. LIMITATIONS OF THE STUDY:

1. The study was conducted using a formulation of thiamethoxam which is not the same as that proposed for Canadian use. The study formulation is a water dispersible granular formulation, and the proposed Canadian formulation is a water-based flowable suspension. The proposed Canadian formulation also contains 3 additional active ingredients, and many other formulants than those in the study formulation.

2. Skin washes were conducted at 6 hrs. A skin wash following a time period representative of worker exposure (i.e., a wash at 10 hrs, representing the end of a work shift) would have been move appropriate.

3. No information was given regarding the storage period of prepared dose suspensions before application, nor of the storage period for samples which were stored before analysis..

4. Residual urine was not collected from the bladder after sacrifice. This means that the amounts of radioactivity excreted in urine is likely an underestimate of the actual amount.

B. CONCLUSIONS:

Dermal absorption of thiamethoxam was determined to be 27.0 % (rounded off from 27.05, highest mean dermal absorption value across all groups). This value is considered to represent the potential cumulative dermal absorption of test material that might occur after a 10 hour dermal exposure. As the study design (i.e., longest collection period was 48 hr) did not permit analysis of the fate of skin bound residues, residues at skin site were included in determination of dermal absorption.

Given the uncertainty regarding actual deposition ($\mu g/cm^2$) of thiamethoxam under field conditions, and the differences in the

test formulation and the proposed end-use formulation (i.e., formulation type, active ingredient composition, formulant composition differences) it was considered appropriate to use a conservative estimate of dermal absorption (i.e., 27%).

Name
Evaluator
Occupational Exposure Assessment Section

Date

Name
Peer Reviewer and Acting Head
Occupational Exposure Assessment Section

Date

Name
Acting Director
Health Evaluation Division

Date

APPENDIX 1 Proposed Canadian Formulation

The formulation proposed for Canadian use is a product called HELIX, and is formulated as follows:

Active ingredient:	thiamethoxam	20.7% weight
	difenconazole	1.25%
	fludioxonil	0.13%
	metalaxyl-M	0.39%

Formulants:

[redacted]

Inert ingredient information may be entitled to confidential treatment

Product ingredient source information may be entitled to confidential treatment

Table 3a: Summary of Results - Low Dose Group

Matrix Analysed	Mean Thiamethoxam Residues (% of dose)[1] Low Dose Group ((2.5 µg/cm²) (ranges provided in brackets)		
Subgroup-sacrifice time	**6ha**	**24h**	**48h**
Urine 0 - 6 h	0.13 (0.01-0.32)	0.74(0.12-2.04)	0.43 (0.02-1.02)
6 - 24 h	-	0.61(0.41-0.91)	0.50 (0.17-0.96)
24 - 48 h	-	-	0.17 (0.10-0.26)
Subtotal	0.13 (0.01-0.32)	1.34 (0.48-2.78)	1.10 (0.31-2.23)
Faeces 0 - 6	0.04 (<0.01-0.15)	<0.01(<0.01-0.01)	0.01 (<0.01-0.04)
6 - 24 h	-	0.06 (0.01 -0.07)	0.05 (<0.01-0.10)
24 - 48 h	-	-	0.05 (0.02-0.10)
Subtotal	0.04 (<0.01-0.15)	0.06 (0.01-0.09)	0.11(0.03-0.18)
Cage Wash	0.09 (0.02-0.29)	0.11 (0.06-0.22)	0.09 (0.01-0.24)
Total Excretion	**0.26(0.03-0.76)**	**1.52 (0.61-3.11)**	**1.31 (0.40-2.63)**
Residues whole blood	<0.01	<0.01	<0.01
untreated skin	<0.01	<0.01	<0.01
carcass	0.17(<0.01-0.69)	<0.01	<0.01
Subtotal	0.18(<0.01-0.69)	<0.01	<0.01
Systemic absorption (excretion + residues)	**0.44** (0.03-1.44)	**1.52 (0.61-3.11)**	**1.31 (0.42-2.63)**
Treated skin	**19.95 (18.21-21.06)**	**19.76 (15.28-22.34)**	**18.31 (17.40-21.57)**
Total absorption (systemic absorption + treated skin)	**20.39 (18.32-21.21)**	**21.28 (15.91-23.82)**	**19.62 (16.59- 23.23)**
Skin wash + O-ring + cover tape[2]	79.34 (77.67-80.77)	75.84 (72.71-82.11)	77.33 (75.74-80.89)
Total Recovery	99.74 (98.89-101.68)	97.12 (95.66-98.02)	96.95 (95.57-98.98)

[1]Values represent mean of results from 4 animals
[2]Although residues and O-ring and cover tape can be interpreted as not available for absorption, and therefore subtracted from the applied dose, the study authors considered these residues available for absorption. As mean values were less than 3% of applied dose, this approach is considerable acceptable.
< values indicate residues were at the Limit of Quantification

Table 3b: Summary of Results - Middle Dose Group

Matrix Analysed	**Mean Thiamethoxam Residues (% of dose)[1] Middle Dose Group ((25.3 µg/cm²) (ranges provided in brackets)**		
Subgroup-sacrifice time	**6h**	**24h**	**48h**
Urine 0 - 6 h	1.75 (0.21-3.98)	0.78 (0.11-1.28)	1.43 (0.11-2.31)
6 - 24 h	-	0.64 (0.45-0.83)	0.89 (0.31-1.46)
24 - 48 h	-	-	0.3 (0.22-0.49)
Subtotal	1.75 (0.21-3.98)	1.42 (0.56-2.11)	2.61 (0.64-4.27)
Faeces 0 - 6	0.05 (<0.01-0.16)	0.02 (<0.01-0.03)	0.05 (<0.01-0.12)
6 - 24 h	-	0.07 (0.02-0.09)	0.07 (0.02-0.10)
24 - 48 h	-	-	0.02 (<0.01-0.03)
Subtotal	0.05 (<0.01-0.16)	0.08 (0.02-0.11)	0.14 (0.03-0.24)
Cage Wash	0.17 (0.06-0.21)	0.12 (0.03-0.18)	0.12 (0.07-0.14)
Total Excretion	**1.97 (0.28-4.46)**	**1.63 (0.61-2.34)**	**2.87 (0.76-4.63)**
Residues whole blood	0.02 (<0.01-0.04)	<0.01	<0.01
untreated skin	<0.01(<0.01-0.02)	<0.01	<0.01
carcass	0.72 (0.17-1.47)	<0.01	<0.01
Subtotal	0.75 (0.19-1.52)	<0.01	<0.01
Systemic absorption (excretion + residues)	**2.72 (0.55-5.98)**	**1.63 (0.61-2.34)**	**2.87 (0.77-4.63)**
Treated skin	**24.33 (19.49-29.22)**	**20.67 (18.43-22.58)**	**20.92 (17.87-24.33)**
Total absorption (systemic absorption + treated skin)	**27.05 (24.36-32.86)**	**22.30 (20.77-24.40)**	**23.79((19.5-27.38)**
Skin wash + O-ring + cover tape[2]	70.23 (63.18-73.17)	75.24(73.35-77.71)	74.42 (70.31-80.05)
Total Recovery	97.29 (96.04-98.17)	97.55 (96.90-98.48)	98.21 (97.53-99.56)

[1]Values represent mean of results from 4 animals

[2]Although residues and O-ring and cover tape can be interpreted as not available for absorption, and therefore subtracted from the applied dose, the study authors considered these residues available for absorption. As mean values were less than 3% of applied dose, this approach is considerable acceptable.

< values indicated residues were at the Limit of Quantification

Table 3c: Summary of Results - High Dose Group

Matrix Analysed	**Mean Thiamethoxam Residues (% of dose)[1] High Dose Group (2423 µg/cm²) (Ranges provided in brackets)**		
Subgroup-sacrifice time	**6h**	**24h**	**48**
Urine 0 - 6 h	0.47 (0.17-0.82)	0.30 (0.10-0.64)	0.25 (0.02-0.44)
6 - 24 h	-	0.22 (0.12-0.38)	0.26 (0.16-0.38)
24 - 48 h	-	-	0.13 (0.10-0.15)
Subtotal	0.47 (0.17-0.82)	0.52 (0.22-1.02)	0.64 (0.31-0.89)
Faeces 0 - 6	<0.01	<0.01	<0.01
6 - 24 h	-	0.02 (<0.01-0.04)	0.03 (0.02-0.04)
24 - 48 h	-	-	<0.01
Subtotal	<0.01	0.02 (<0.01-0.04)	0.04 (0.02-0.07)
Cage Wash	0.08 (0.02 -0.14)	0.03 (0.01-0.08)	0.07 (0.02-0.18)
Total Excretion	**0.56 (0.19-0.97)**	**0.58 (0.24-1.14)**	**0.75 (0.35-1.11)**
Residues whole blood	<0.01	<0.01	<0.01
untreated skin	<0.01	<0.01	<0.01
carcass	0.14 (<0.01-0.30)	0.01 (<0.01-0.05)	<0.01
Subtotal	0.15 (<0.02-0.30)	0.01 (<0.01-0.05)	<0.01
Systemic absorption (excretion + residues)	**0.71 (0.20-1.27)**	**0.59 (0.25-1.20)**	**0.76 (0.35-1.11)**
Treated skin	**4.56 (3.86-5.18)**	**3.96 (3.21-4.83)**	**3.76 (3.35-4.07)**
Total absorption (systemic absorption + treated skin)	**5.27 (4.43-6.45)**	**4.55 (3.46-6.03)**	**4.52 (4.35-4.65)**
Skin wash + O-ring + cover tape[2]	91.19 (88.84-92.40)	90.65 (86.31-92.61)	90.59 (89.62-92.16)
Total Recovery	96.46 (93.71-97.88)	95.2 (90.87-98.06)	95.11 (93.98-96.82)

[1]Values represent mean of results from 4 animals

[2]Although residues and O-ring and cover tape can be interpreted as not available for absorption, and therefore subtracted from the applied dose, the study authors considered these residues available for absorption. As mean values were less than 3% of applied dose, this approach is considerable acceptable.

< values indicated residues were at the Limit of Quantification

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