

US EPA ARCHIVE DOCUMENT

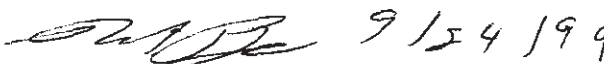
Data Evaluation Report

Chemical Oxadiazin

014525

Study Type Dermal absorption (GL 85-3)Citation

The in vitro percutaneous absorption of [Oxadiazin-4-¹⁴C] CGA 293343 Formulated as WG 25 (A-9584C) through Rat and Human Epidermis. K.E. Mewes. Novartis Crop Protection AG. Study No 027AM08. Novartis Nexus Number 969-98. Aug 13, 1998. MRID 447034-08

 9/24/99
Reviewed by Robert P. Zendzian PhD
Senior Pharmacologist

Core Classification Invalid (an invalid procedure which cannot be upgraded)Summary

This study utilized the isolated epidermal membrane from rat and human skin. Membranes were prepared by soaking in 2M aqueous NaBr (rat) or in 60°C water for 1 minute (human). Membranes were mounted in flow through cells for 48 hours of exposure. Doses were 22, 189 or 2645 ug/cm² in the rat and 22, 193 or 2638 ug/cm² in the human. Results are presented in Table 13 from the report (attached).

Adequate experimentally derived information are available to the Office of Pesticide Programs to allow assessment of the validity of this procedure. Comparative *in vitro* and *in vivo* studies show that the procedure rarely accurately follows the *in vivo* results. *In vitro* may over or under estimate the *in vivo* values even for the same chemical, in the same species, in the same laboratory. Errors are unpredictable and have ranged as high as seven fold. The procedure is clearly shown to be unable to accurately match *in vivo* values and is invalid. The error is intrinsic and the procedure cannot be corrected.

Table 13 Mean cumulative penetration of [Oxadiazin-4-¹⁴C] CGA 293343 through rat and human epidermis (% of dose)

Cumulative penetration [% of dose]						
Species	rat			human		
Group	Q1			Q2		
Dose level	A1	A2	A3	A1	A2	A3
Applied Dose [$\mu\text{g}\cdot\text{cm}^{-2}$]	22	189	2645	22	193	2638
Number of replicates	5	7	6	7	6	7
Time period						
0 - 1 h	0.3	1.1	0.9	0.01	< 0.01	< 0.01
0 - 2 h	1.6	4.0	3.3	0.2	0.1	0.05
0 - 3 h	4.2	9.7	5.9	1.4	0.4	0.4
0 - 4 h	9.9	17.9	8.3	4.0	1.2	1.2
0 - 5 h	14.9	23.1	10.5	8.5	2.8	1.6
0 - 6 h	17.8	25.9	12.7	12.0	4.0	1.8
0 - 8 h	20.0	28.6	16.7	17.3	6.0	2.1
0 - 10 h	21.1	29.6	20.3	20.2	6.9	2.3
0 - 12 h	22.1	30.5	23.0	21.7	7.6	2.4
0 - 14 h	23.0	31.1	25.3	22.6	8.0	2.4
0 - 16 h	23.8	31.6	27.4	23.0	8.3	2.5
0 - 18 h	24.5	32.0	29.2	23.3	8.5	2.5
0 - 20 h	25.1	32.5	30.8	23.6	8.7	2.5
0 - 22 h	25.6	32.8	32.3	23.8	8.8	2.5
0 - 24 h	26.1	33.2	33.5	23.9	8.9	2.5
0 - 28 h	27.0	34.9	36.1	24.3	9.1	2.5
0 - 32 h	27.7	36.4	38.2	24.6	9.2	2.5
0 - 36 h	28.4	37.4	40.2	24.9	9.3	2.5
0 - 40 h	29.3	38.2	41.8	25.1	9.4	2.5
0 - 44 h	30.2	38.9	43.2	25.4	9.5	2.5
0 - 48 h	30.8	39.6	44.2	25.6	9.6	2.6

[PMRA Sub. No.98-1541/Novartis] ~ PROTECTED ~
 [Thiamethoxam] / PMRA Sub.No 98-1541]

Rodent *In vitro* Dermal Absorption Study
 DACO 5.8 / OECD 7.6.1



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

STUDY TITLE: The *in vitro* Percutaneous Absorption of [Oxadiazin-4-¹⁴C] CGA 293343 Formulated as WG 25 (a-9584C) in through Rat and Human Epidermis

STUDY TYPE: *In vitro* Dermal Absorption using Rat and Human Epidermis

TEST MATERIAL:

Company Code: CGA 293343
 Common name: Thiamethoxam
 Trade name: Conquest 24 WG/ACTARA 25WG
 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: C₈H₁₀ClN₅O₃S

SYNONYMS: Thiamethoxam technical

CITATION: Mewes, K.E.. 1998. The *in vitro* Percutaneous Absorption of [Oxadiazin-4-¹⁴C] CGA 293343 Formulated as WG 25 (a-9584C) in through Rat and Human Epidermis. NOVARTIS Crop Protection AG, Basel, Switzerland. Study 027AM08 August 13, 1998. MRID 44703408.

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

EXECUTIVE SUMMARY:

Dermal absorption of thiamethoxam formulated as a wettable granule was evaluated *in vitro* (flow-through diffusion cells), using non-viable epidermal preparations of rat and human origin. Three dose levels were used: 22 µg/cm²; 189-193 µg/cm² and 2638-2645 µg/cm². Five to seven replicates were used per species per dose level. Skin preparations were determined to be of adequate integrity. Thiamethoxam was analyzed in the receptor cell at regular intervals over 48 hrs. At 48 hrs, skin sites were washed and residues were analyzed in donor cell wash, receptor cell wash, skin rinse, and epidermis. Percent dermal absorption was determined by summing cumulative thiamethoxam residues in the receptor cell, the receptor cell wash, and the epidermis. Recoveries ranged from 99.1 to 113.8%. Mean dermal absorption in the rat epidermis was 81.2% (low dose), 46.2% (middle dose) and 48.8% (high dose). Mean dermal absorption in the human epidermis was 29.1% (low dose), 10.2% (middle dose) and 3.1% (high dose).

[PMRA Sub. No.98-1541/ Novartis] ~ PROTECTED ~
 [Thiamethoxam] / PMRA Sub.No 98-1541]

Rodent *In vitro* Dermal Absorption Study
 DACO 5.8 / OECD 7.6.1

It is recognized that *in vitro* dermal absorption studies, alone, are not sufficiently validated for use in deriving estimates of systemic exposure for risk assessments (draft NAFTA Harmonization Position Paper on Methodology Issues, January, 18, 1999). As such, the results of this study are of limited utility. Furthermore, although data from a well-conducted *in vitro* study may have some utility (e.g., as bridging data between species), a significant limitation of this study design was the use of nonviable skin. The results, however, do suggest that thiamethoxam is readily absorbed through rat and human skin, and that dermal absorption may be higher in rats than in humans.

WAS AN IN VIVO DERMAL ABSORPTION STUDY SUBMITTED: Yes

GUIDELINE OR PROTOCOL FOLLOWED: This study was conducted according to the draft OECD Guideline for Testing of Chemicals, Dermal Delivery and Percutaneous Absorption: *In Vitro* Method, 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
 Tradename: Conquest 24 WG/ACTARA 25WG
 Lot/Batch #: Radiolabelled test substance: ILS-194.1
 Non-radiolabelled test substance: AMS 780/102
 Purity: Radiolabelled test substance: 99.8%
 Non-radiolabelled 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 μ Ci/mg (The radiolabelled test substance was diluted with non-radiolabelled substance at the high dose to give a specific activity of 31.6kBq/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 than the test formulation. Key differences are outlined below:

[PMRA Sub. No.98-1541/ Novartis] ~ PROTECTED ~
 [Thiamethoxam) / PMRA Sub.No 98-1541]

Rodent *In vitro* Dermal Absorption Study
 DACO 5.8 / OECD 7.6.1

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%	██████
Diluent	60% corn start	██████████

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 Membranes:

Rat Skin

Species and Strain: Tif: RAI f (SPF) rat skin was utilized in this in vitro study. This is the same strain that was used in the *in vivo* rat dermal absorption study which was also conducted with the same formulation of thiamethoxam.

Gender: male

Age: rats were 23-25 days old when epidermis was harvested.

Source: Biological Research Laboratories (BRL), Fullinsdorf, Switzerland

Housing: Rats were kept polycarbonate cages

Diet: Animals were allowed free access to the certified standard diet

Water: Tap water was offered *ad libitum* at all times

Sacrifice: Within 24 hours after arrival, rats were sacrificed by an overdose of carbon dioxide gas in a desiccator

Storage: Stored at -18 °C until preparation of the epidermis

Human skin

Site: abdominal cadaver skin

Gender and age: female Caucasian - 68 years of age (used for all three dose levels)
 male Caucasian - 74 years of age (used for all three dose levels)

Source: International Institute for the Advancement of Medicine, Exton, Pennsylvania, U.S.

Storage: The skin was received frozen and stored at -18°C until preparation of the epidermis.

Inert ingredient information may be entitled to confidential treatment

US EPA ARCHIVE DOCUMENT

[PMRA Sub. No.98-1541/Novartis] ~ PROTECTED ~
 [Thiamethoxam] / PMRA Sub.No 98-1541]

Rodent *In vitro* Dermal Absorption Study
 DACO 5.8 / OECD 7.6.1

B. METHODS

1. Dose

Rationale: The low dose formulation was chosen to represent a typical concentration recommended for use in the field (i.e. 50 g ai/200L applied to 1 ha). The middle and high doses represent exaggerated use conditions. 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: Actual doses were determined by analyzing radioactivity of three control doses.

rat skin: 22, 189, 2645 $\mu\text{g}/\text{cm}^2$

human skin: 22, 193, 2638 $\mu\text{g}/\text{cm}^2$

(Note: the low and middle dose levels are comparable to the middle and high dose levels of the *in vivo* rat study)

Dose volume: A 50 μL aliquot was applied to the donor chamber of each diffusion cell using a pipette.

2. Dose 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). The formulations were prepared separately for all dose groups.

To prepare the stock solutions, [Oxadiazin-4- ^{14}C]-labelled thiamethoxam was dissolved in dichloromethane. Aliquots were then checked for radiocarbon content and the concentration of the stock solution determined by Liquid Scintillation Counting (LSC). An appropriate volume of the radiolabelled stock solution was then added to the blank formulation to create the dose. After homogenisation, the solvent was removed by evaporation. Prior to dose administration, the formulated test substance was mixed with water.

For the high dose only radiolabelled thiamethoxam was mixed with unlabeled stock solution. Unlabelled stock solution was prepared the same way as the labelled stock, to yield a concentration of 10 mg/mL. The volumes of stock solution and blank formulation utilized for the applied dose levels are outlined in Table 1.

Each cell received a 50 μL aliquot of the application solution using a pipette. The actual amount applied to the cells was determined by analysis of control dosings (note: this data was not provided in the study report).

Table 1 Dose Preparation

Dose Group	Stock Solution	Water Volume (μL)	Actual Applied Dose			
			kBq/cell	mg/cell ¹	$\mu\text{g}/\text{cm}^2$ ²	Conc. ($\mu\text{g}/\text{cm}^3$)
Low rat: human:	doses were prepared by diluting 150 μL of the middle dosing solutions	1350	27.8 27.7	0.014 0.014	22 22	286 285
Middle rat: human:	1.85 mg ^{14}C -thiamethoxam 3.7 mg ^{14}C -thiamethoxam	743 1485	234.8 239.1	0.121 0.123	189 193	2420 2465

[PMRA Sub. No.98-1541/ Novartis] ~ PROTECTED ~
 [Thiamethoxam] / PMRA Sub.No 98-1541]

Rodent *In vitro* Dermal Absorption Study
 DACO 5.8 / OECD 7.6.1

High rat:	33.5 mg unlabelled thiamethoxam +	1364	53.5	1.693	2645	33854
human:	0.555mg ¹⁴ C-thiamethoxam		53.3	1.688	2638	33765

¹ 50 µL aliquot was applied to each cell

² Application was made to 0.64 cm² epidermis

3. Number of replicates: Each diffusion cell was considered as one replicate. For rat epidermis, 5 cells were used at the low dose level; 7 cells at the middle dose level; and 6 at the high dose level. For human epidermis, 7 cells were used at the low and high dose level; and 6 cells at the middle dose level.

4. Skin Preparation

Preparation of Rat Epidermis: After sacrifice, the abdominal skin was clipped, and the full thickness skin excised. The skin was wrapped in aluminum foil and stored at -18°C. The study report did not mention the duration of storage. To separate the epidermis, the skin was soaked in aqueous sodium bromide solution for approximately 18 hours. The skin was blotted dry, and the epidermis carefully peeled away from the dermis. The epidermis was wrapped in aluminum foil and stored at 4°C for approximately 3 days.

Preparation of Human Epidermis: The human skin sample was removed from the freezer and thawed at room temperature. Sections of skin approximately 10 cm² were immersed into hot water (approx. 60°C) for about 1 minute. The skin was blotted dry and the epidermis carefully peeled away from the dermis. The epidermis was used immediately.

Membrane Integrity/Viability: The integrity of the epidermal membranes was checked by applying 50 µL tritium water to the epidermal surface. The donor chamber was occluded with Parafilm, and penetration was determined cumulatively over 6 hours. The permeability coefficient (K_p) of each membrane was calculated for the 3-6 hour interval. Rat epidermis with $K_p > 3.5 \times 10^{-3}$ cm/hr and human epidermis with $K_p > 2.5 \times 10^{-3}$ cm/hr were excluded from the experiment. After 6 hours, the remaining tritium water was removed from the epidermal surface with a tissue and the cells were left overnight with the saline flowing through the receptor chamber.

Skin viability was not demonstrated. Skin was considered non-viable as samples were frozen prior to use.

5. Diffusion Cell Apparatus:

Description: Fourteen flow-through diffusion cells were placed in two aluminum manifolds (7 cell systems in each manifold), each connected to a water bath designed to maintain the epidermis at 32°C. Each diffusion cell consisted of a donor and receptor chamber. The area of epidermis exposed to the donor chamber was 0.64 cm². The receptor chamber was connected to a multi-channel peristaltic pump (model IPC-16). The pump speed was set at 3 mL/hour, and the effluent from the cell was collected directly into vials on a fraction collector (model ISCO retriever IV).

Set-Up: Circles of the epidermal membranes (approx. 1.8 cm diameter) were cut and mounted in the diffusion cells between the donor and receptor chamber. The stratum corneum was exposed to the air and the basal membrane of the epidermis was in contact with the receptor fluid. The cells were placed in the temperature controlled manifolds, and connected to the peristaltic pump. During the equilibration period (0.5-1 hour), a solution of saline and hydrochloride was pumped through the receptor chamber at a flow rate of 3 mL/h.

6. Application Procedure

Application of dose: The receptor fluid was changed to ethanol/water (1:1 v/v) and delivered at a flow rate of 3 mL/h. Cells were arranged on one manifold, and a 50µL aliquot of the formulated dose was applied to the epidermal surface. The donor chamber of the diffusion cell was left open (non-occluded). The perfusates were collected at ambient temperatures at the

[PMRA Sub. No.98-1541/ Novartis] ~ PROTECTED ~
 [Thiamethoxam] / PMRA Sub.No 98-1541]

Rodent *In vitro* Dermal Absorption Study
 DACO 5.8 / OECD 7.6.1

following time intervals:

- 0 - 6 hours: 1 hour intervals
- 6-24 hours: 2 hour intervals
- 24 - 48 hours: 4 hour intervals

Wash Procedure: 48 hr after application the epidermal surface was rinsed with ethanol/water (1:1 v/v)

Termination period: 48 hr

7. Sample Preparation and Analysis:

Sample Collection and Preparation: Upon collection, liquid samples (i.e., perfusate, skin rinse, donor cell wash, receptor cell wash) were added directly to the scintillation mixture for analysis, as described below. Immediately following the 48 hr skin wash, epidermal membranes were removed from the cell chambers. Epidermal samples were digested using a Soluene-350 solubilizer. Digested specimens were then neutralized with hydrochloric acid.

Radioactivity: Radioactivity was measured using LSC on Packard Tri-Carb scintillation counters (model 2000CA) equipped to compute quench-corrected dpm. Liquid samples were added directly to the scintillation mixture Irga-Safe plus for analysis. Digested, neutralized epidermal specimens were mixed with Irga-Safe plus for analysis. Background values were measured for each sample run using the respective scintillation mixture with no sample. Limits of Quantification were provided for the receptor fluid perfusate; these ranged from 0.003 to 0.2168 $\mu\text{g}/\text{cm}^2$. Limits of Quantification were not provided for the other matrices.

Thin layer chromatography (TLC): The purity of the formulated test substance and the stability of the skin rinse was determined using thin layer chromatography (TLC) and acetonitrile/water/formic acid (90/5/5 v/v/v) or methylethylketone/methanol (80/20 v/v) solvents. Radioactivity patterns and zones were detected and quantified on thin layer plates using a Bio-Imaging Analyser, model BAS 2000, and the images were processed further using TINA software. Limits of Quantification were not provided for this method.

II. RESULTS

1. Radiochemical Purity: Radiochemical purity was considered adequate. Analyses of rinsate from the skin of rats and humans showed that more than 97% of the radioactivity was attributable to thiamethoxam, except for the human high dose group, where 85% of the recovered radioactivity was attributable to thiamethoxam. Because no degradation products could be identified on the chromatogram, study authors concluded that the lower purity of this dose group was likely due to a poor signal to noise ratio.

2. Stability: The radiolabelled compound was determined to be stable. TLC analysis of the application solutions showed that the formulated test substance was stable at the time of application. At all three dose levels, the radiolabelled thiamethoxam represented at least 98% of the radioactivity.

3. Integrity/Viability of Tissue Samples: The epidermal samples used in the study were demonstrated to be of acceptable integrity. Results showed that the mean permeability coefficient of tritium water was $2.09 \pm 0.73 \times 10^{-3}$ for rat epidermis, and $0.96 \pm 0.22 \times 10^{-3}$ for human epidermis. All results were within the acceptable limits, therefore none of the test membranes were excluded from the experiment.

The epidermal samples were not subject to a test of tissue viability, and were considered nonviable as they had been frozen prior to use.

4. Recovery: Mean recoveries were 99.1 to 113.8% and were considered acceptable.

5. Dermal Absorption Parameters: Although the study report provided calculations of kinetic parameters including

[PMRA Sub. No.98-1541/ Novartis] ~ PROTECTED ~
 [Thiamethoxam) / PMRA Sub.No 98-1541]

Rodent *In vitro* Dermal Absorption Study
 DACO 5.8 / OECD 7.6.1

absorption rate, permeability coefficient and lag time, the relevant result with respect to occupational exposure assessment is dermal absorption represented as a % of applied dose. This was determined by summing thiamethoxam residues in perfusate over the 48 hour collection period, in receptor cell wash and epidermis and dividing by the applied dose. Results are provided in Table 2.

Table 2: Summary Results

Matrix	Mean Thiamethoxam Residues in Matrix (% dose)					
	Rat			Human		
	Low(n=5)	Middle (n=7)	High (n=6)	Low (n=7)	Middle (n=6)	High (n=7)
Dose($\mu\text{g}/\text{cm}^2$)	22	189	2645	22	193	2638
Perfusate (0-48 hr)	30.8 SD 12.2	39.6 SD 14.8	44.2 SD 28.2	25.6 SD 9.9	9.6 SD 3.8	2.6 SD 1.0
Donor Cell Wash	1.8 SD 0.5	0.6 SD 0.1	0.9 SD 0.7	0.3 SD 0.1	0.1 SD 0.2	0.4 SD 0.3
Receptor Cell Wash	5.0 SD 2.5	1.3 SD 0.5	2.5 SD 2.9	0.6 SD 0.4	0.1 SD 0.01	0.1 SD 0.1
Skin Rinse	46.9 SD 14.1	58.4 SD 14.7	49.4 SD 25.5	71.4 SD 11.7	103.5 SD 9.7	100.0 SD 8.7
Epidermis	14.6 SD 4.6	5.3 SD 1.8	2.1 SD 1.7	2.9 SD 0.9	0.5 SD 0.05	0.4 SD 0.5
Dermal Absorption	81.2	46.2	48.8	29.1	10.2	3.1
Recovery	99.1	105.1	99.1	100.8	113.8	103.4

SD=standard deviation

III. DISCUSSION

A. LIMITATIONS OF THE STUDY:

- As noted in the draft NAFTA Harmonization Position Paper on Methodology Issues (January, 18, 1999), PMRA and U.S. EPA are in agreement that *in vitro* dermal absorption studies, alone, are not sufficiently validated for use in deriving estimates of system exposure for risk assessments. As such, the results of this study are of limited utility.
- Although data from a well-conducted *in vitro* study may have some utility (e.g., as bridging data between species), a limitation of this study design was that nonviable skin was used. This further limits the use of the results.
- 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.
- The significant variability associated with analysis of perfusate and skin rinse among replicates for a given species-dose level limit confidence in results.

[PMRA Sub. No.98-1541/ Novartis] ~ PROTECTED ~
[Thiamethoxam) / PMRA Sub.No 98-1541]

Rodent *In vitro* Dermal Absorption Study
DACO 5.8 / OECD 7.6.1

- 5. A skin wash was conducted at 48 hrs only, just prior to sacrifice. 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 more applicable.

B. CONCLUSIONS

The study design (e.g., *in vitro* methodology, use of nonviable skin) preclude the use of this data in a quantitative manner. The results, however, do suggest that thiamethoxam is readily absorbed through rat and human skin, and that dermal absorption may be higher in rats than in humans.

 Name
 Evaluator
 Occupational Exposure Assessment Section

 Name
 Peer Reviewer and Acting Head
 Occupational Exposure Assessment Section

Date

Date

 Name
 Acting Director
 Health Evaluation Division

Date