



Winston H. Hickox  
Secretary for  
Environmental  
Protection

# Department of Pesticide Regulation

830 K Street • Sacramento, California 95814-3510 • www.cdpr.ca.gov



Gray Davis  
Governor

## MEMORANDUM

TO: Gary Sprock, Registration Specialist  
Pesticide Registration Branch  
HSM-99012

FROM: Tom Thongsinthusak, Staff Toxicologist  
Worker Health and Safety Branch  
(916) 445-4267

DATE: April 7, 1999

SUBJECT:  
BRAND NAME: Guthion  
ACTIVE INGREDIENT: Azinphos-methyl  
COMPANY NAME: Bayer Corporation  
I.D. NUMBER: 176369-E  
RECORD NUMBER (RN): 167193  
DATA PACKAGE NUMBER (DPN): 154-307  
EPA REGISTRATION NUMBER: 3125-0-  
TITLE: ABSORPTION, EXCRETION, BALANCE AND PHARMACOKINETICS OF <sup>14</sup>C  
RADIOACTIVITY AFTER SINGLE DOSE DERMAL APPLICATION OF THREE  
DOSE LEVELS OF <sup>14</sup>C LABELED GUTHION TO HEALTHY VOLUNTEERS

---

The above human dermal absorption study (DPN 154-307, RN 167193) was initiated on May 7, 1998 and completed on February 17, 1999. The submitted report indicated that this study was conducted in accordance with these practices and guidelines: "Clinical portion" – Good Clinical Practice Regulations, Declaration of Helsinki, W.H.O Principles for the Clinical Evaluation of Drugs, FDA General Considerations for the Clinical Evaluation of Drugs; "Analysis" – FDA Good Laboratory Practice for Non-Clinical Laboratories Studies, OECD principles of Good Laboratory Practice (GLP); "Study conducted at Bayer AG" - OECD principles of GLP; "Studies conducted at XenoBiotic Laboratories" – FIFRA GLP (40 CFR, part 160). The Quality Assurance (QA) statement for "XBL Study No. 98052" was included in the report. However, this report did not show a QA statement for the in-life portion according to the U.S. EPA GLP standards, 40 CFR, part 160.35 (b) (7); this part requires a signed QA statement which specifies the dates of inspections and findings reported to management and to the study director. Details of test conditions for the dermal penetration study of azinphos-methyl using

eighteen healthy human volunteers are shown in Table 1. These qualified volunteers passed strict selection criteria. They stayed in the clinical research facility and were provided with medical exams, standardized meals, and monetary compensation.

Table 1. Details of test conditions used in the study of <sup>14</sup>C-azinphos-methyl in healthy human volunteers.

Test conditions	Details
Azinphos-methyl	(Phenyl Ring-U- <sup>14</sup> C)-azinphos-methyl, purity 98.9% (97.5% for 25 WP formulation), MW 317.3
Dose preparation (nominal)	a) In isopropyl alcohol (IPA): 72.8 and 240 µg a.i./100 µL. b) Aqueous suspension of Gusathion M WP 25: <i>ca</i> 120 µg a.i./100 µL.
Volunteers/group	Six volunteers/group or 18 volunteers/3 groups.
Body weight	Group 1: 71.7-88.2 (79.9 ± 5.9) kg; Group 2: 63.5-86.4 (73.9 ± 8.2) kg; Group 3: 64.6-93.8 (76.5 ± 10.6) kg.
Actual dose (µg a.i./cm <sup>2</sup> )	Group 1 (2.6, in IPA), Group 2 (9.2, in IPA), group 3 (4.7, as aqueous suspension of the 25 WP formulation). A total applied volume was 100 µL/volunteer.
Application site	Non-shaven area (4 x 6 cm) of the volar aspect of the right or left (non-dominant) forearm. The site was surrounded by an adhesive template. An indwelling venous catheter was placed in both arms for simultaneous collection of blood.
Site protection	The application site was covered with an aluminum dome, which was secured in place with an adhesive bandage. The dome had air holes.
Exposure time	8 hours (h)
Cleaning of the application site	Groups 1&2: The application site was cleaned with 16 cotton swabs dipped in IPA. The site was then thoroughly rinsed with a steady stream of IPA. Group 3: Used 2% solution of Unicura <sup>®</sup> liquid soap instead of IPA.
Collection of samples	Urine and feces were collected for up to 312 h and blood for up to 120 h.
Tape stripping	The applied site was divided into 6 equal sections. Forty five hours after removal of the dose, each section was stripped 16 times using adhesive cellophane tape.
Blood samples (10 mL each)	Samples were collected 0 (predose), 2, 4, 8, 6, 10, 12, 16, 24, 36, 48, 72, 96, and 120 h after the application of the dose.
Urine samples	Collected at predose, 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, and every 24 hours after the application of the dose or until the radioactivity in 1 mL of urine was less than twice the background count.
Feces samples	Predose and in 120 h or until the radioactivity in 400 mg of homogenized feces was less than 75 DPM.
Analysis	Prepared samples were analyzed by Beckman liquid scintillation spectrophotometers.

The clinical portion of the study was conducted at Pharma Bio-Research Clinical Research Center, The Netherlands. All eligible human volunteers read and signed an informed consent form prior to being enrolled into the study.

XBL (Plainsboro, New Jersey) conducted the radioanalysis of the dosing solutions, the applicators, application site protective enclosures, swabs, application site rinsates, protective gauze, tape strippings, plasma, red blood cells, urine, and feces. Bayer AG (Germany) performed the analysis of cholinesterase activity (plasma and red blood cells).

According to the report, all human volunteers enrolled in the study completed the study process. No serious events were observed during the conduct of the study. All clinical data for those volunteers were considered normal as determined by an attending physician. The dose was well tolerated by volunteers and no abnormalities were observed on the application site. But, eight out of 18 volunteers reported a total of nine adverse events. Those events were pain or haematoma on the site of the IV cannula used for blood sampling (3 reports), myalgia (2 reports), and tiredness, eczema of one finger, and one loose stool. The attending physician considered all adverse events to be unrelated to the test material.

Dermal absorption data: Results of the dermal absorption study of azinphos-methyl are shown in Table 2. The dermal absorption was determined as the sum of the percentage of the applied dose recovered in urine, feces, and tape stripping samples. The majority of the absorbed dose was excreted in the urine. The excretion in the feces was about eight-fold lower than that in the urine. The percentage of the applied dose recovered in tape stripping was minimal.

It was apparent that azinphos-methyl was not accumulated in the human body during the study period because the percentage of the total recovery of the dose was high, averaging 105.4, 102.5, and 101.9% for groups 1, 2, and 3, respectively. The average recovery for each dose was used to correct the percentage of dermal absorption. The mean dermal absorption values for group 1 ( $2.6 \mu\text{g}/\text{cm}^2$ ), group 2 ( $9.2 \mu\text{g}/\text{cm}^2$ ), and group 3 ( $4.7 \mu\text{g}/\text{cm}^2$ ) were  $27.8 \pm 13.0$ ,  $22.9 \pm 12.6$ ,  $21.5 \pm 9.6\%$ , respectively.

The mean concentration of radioactivity in plasma reached the maximum count (DPM/mL) at about 10 h post application of the dose (Table 3), indicating a fairly rapid absorption and translocation of azinphos-methyl in human body. However, the mean percentage of radioactivity in red blood cells (Group 2) reached the maximum count at about 120 h post application of the dose. Group 2 was the only group that the radioactivity in red blood cells was determined.

Table 2. Dermal absorption of azinphos-methyl in human volunteers.

Group 1 (2.6 ug/cm<sup>2</sup>, 14C-Guthion a.i. in IPA)

Sample/volunteer	% Dose						Mean	SD
	1	2	3	4	5	6		
Urine	20.86	16.6	24.36	45.18	12.7	34.64	25.72	12.14
Feces	2.62	2.42	3.12	5.68	1.66	4.31	3.30	1.46
Tape stripping	0.18	0.07	0.27	0.47	0.27	0.55	0.30	0.18
Absorbed	23.66	19.09	27.75	51.33	14.63	39.5	29.33	13.73
Recovery (%)								105.36
Adjusted dermal absorption (%)							Mean	<b>27.8</b>
							SD	<b>13.0</b>

Group 2 (9.2 ug/cm<sup>2</sup>, 14C-Guthion a.i. in IPA)

Sample/volunteer	% Dose						Mean	SD
	1	2	3	4	5	6		
Urine	30.09	13.12	10.21	14.6	39.44	18.46	20.99	11.39
Feces	3.66	1.38	0.64	1.43	4.82	2.25	2.36	1.58
Tape stripping	0.08	0.33	0.25	0.04	0.07	0.13	0.15	0.12
Absorbed	33.83	14.83	11.1	16.07	44.33	20.84	23.50	12.90
Recovery (%)								102.46
Adjusted dermal absorption (%)							Mean	<b>22.9</b>
							SD	<b>12.6</b>

Group 3 (4.7 ug/cm<sup>2</sup>, aqueous suspension of a.i. as 25 WP)

Sample/volunteer	% Dose						Mean	SD
	1	2	3	4	5	6		
Urine	16.36	14.77	34.56	16.54	9.91	23.2	19.22	8.64
Feces	3.19	2.06	4.8	3.16	0.78	1.57	2.59	1.43
Tape stripping	0.1	0.06	0.16	0.1	0.04	0.03	0.08	0.05
Absorbed	19.65	16.89	39.52	19.8	10.73	24.8	21.90	9.78
Recovery (%)								101.88
Adjusted dermal absorption (%)							Mean	<b>21.5</b>
							SD	<b>9.6</b>

Table 3. Mean radioactivity in plasma samples showing maximum (Maximum) values and radioactivity in last (Last) samples collected for analysis.

Group (Dose)	Mean radioactivity (DPM/mL)			
	Contralateral arm vein		Ipsilateral arm vein	
	Maximum (h)	Last (h)	Maximum (h)	Last (h)
1 (2.6 ug/cm <sup>2</sup> )	83 (10)	38 (120)	130 (10)	42 (120)
2 (9.2 ug/cm <sup>2</sup> )	281 (12)	130 (120)	429 (10)	152 (120)
Red blood cells	247 (120)	247 (120)	174 (12&240)	129 (120)
3 (4.7 ug/cm <sup>2</sup> )	140 (10)	47 (120)	189 (6)	49 (120)

Cholinesterase values for human volunteers are shown in Table 4. In general, the cholinesterase values for pseudo-cholinesterase in plasma, acetylcholinesterase in erythrocyte (CHEE), and CHEE per gram of hemoglobin are in the normal range. Normal ranges for these enzymes are shown in footnotes of Table 4.

Table 4. Cholinesterase values for human volunteers in groups 1 and 2\*.

Dermal dose	Time (h)	PCHE (kU/L)	CHEE (kU/L)	CEHB (U/g)
72 ug a.i.	0	5.37	7.09	24.1
	2-120	5.21-5.03	7.34-7.99	25.1-27.2
240 ug a.i.	0	5.65	6.28	21.3
	2-120	5.46-5.66	6.47-7.59	21.4-27.1

PCHE: Pseudo-cholinesterase in plasma (normal range 3.5 to 8.5 kU/L)

CHEE: Acetylcholinesterase in erythrocytes (normal range 5.26-9.62 kU/L)

CEHB: CHEE per gram of hemoglobin (normal range 23.5 to 32.9 U/g)

\* Samples for group 3 were not analyzed because the samples were sent to a wrong place.

### Conclusions:

1. There was a slight increase in the dermal absorption when the dose was decreased from  $9.2 \mu\text{g}/\text{cm}^2$  to  $2.6 \mu\text{g}/\text{cm}^2$ . It appears that the dose levels used in the study had minimal effects on dermal absorption.
2. IPA might enhance the dermal absorption of azinphos-methyl. IPA is not typically used as a carrier in a pesticide application.
3. An aqueous suspension of azinphos-methyl in the 25 WP formulation is more representative to a normal pesticide application. The dermal absorption of this formulation was in the same range as those when IPA was used as a carrier.
4. Azinphos-methyl was readily absorbed and translocated in the body of human volunteers. The maximum excretion was reached in about 10 h post application of the dermal dose.
5. The measured values of pseudo-cholinesterase in plasma and acetylcholinesterase in erythrocyte were in normal ranges for the dermal doses tested.

### Recommendation:

An average dermal absorption value of 21.5% is recommended for use in the calculation of absorbed dose of azinphos-methyl.

cc: John Ross  
Tareq Formoli

(Dermal/HSM990012)