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State of California

M e m o r a n d u m

To: Gary Varnado, Registration Specialist
Pesticide Registration Branch

Date: December 5, 1996

Place: Sacramento

445-4267

From: Department of Pesticide Regulation -Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch
[original sigend by Tom Thongsinthusak]

Subject: PRODUCT NAME: Garlon™ 4
ACTIVE INGREDIENT: Triclopyr, triethylamine salt
COMPANY NAME: DowElanco
I.D. NUMBER: 134073-E
DOCUMENT NUMBER: 417-073
EPA REGISTRATION NUMBER: 62719-0-
TITLE: Human Dermal Absorption Study of Garlon™ 4 (A Herbicide)

Dermal absorption study in human volunteers:
The subject report was previously submitted to the Department (Carmichael *et al*., 1988). The results of this study were also published in a scientific journal (Carmichael *et al*., 1989). Rech (1989) previously reviewed results of the submitted report and concluded that dermal absorption values ranged from 0.26% to 3.1%, with a mean value of 1.6%. The conclusion was the same as that summarized in the submitted report.

The nominal dose used in this human dermal absorption study was 5 mg/kg body weight. The actual administered dose was 3.5 mg/kg equivalent to 4.8 mg/cm^2. Further comparison of the dose used in this study with other human dermal absorption studies showed that the dermal dose is extremely high. It is also high compared to the average actual dermal exposure of approximately 37 µg triclopyr-butoxyethyl ester (BEE)/cm^2 or 27 µg triclopyr/cm^2 (Middendorf, 1995). From our experiences in evaluating dermal absorption studies of pesticides in animals, dermal absorption values of the majority of pesticides are inversely proportional to dose. Consequently, the dermal absorption of triclopyr was estimated from two field exposure studies.

Exposure monitoring study of triclopyr (Rankin *et al*., 1991):
The first study (Rankin *et al*., 1991, Org # GHS-C-57) was designed to evaluate the occupational exposure of workers to triclopyr during mixing/loading and foliar spray application of Garlon™ 4 herbicide for brush control along industrial-rights-of-way. This study was conducted in Westlock, Alberta, Canada, employing 12 applicators. The tank mix was prepared at the maximum recommended label rate of 7.5 liters of Garlon™ 4 herbicide in a final mixed volume of 1,000 liters. Truck-mounted, motorized, high volume, ground application equipment was used in the spray application. Each worker sprayed an average of 950 liters of diluted spray solution, equivalent to 3.18 kg of triclopyr acid on an average 8.8-hour workday.

The study measured both dermal and inhalation exposure. Both potential dermal and dermal exposures were measured by affixing absorbent cotton-duct patches (100 cm^2) to both inner and outer coveralls at different body regions and hand washes. The inhalation exposure was estimated by monitoring air-borne concentrations of triclopyr near the workers' personal breathing zone. The sampling device consisted of 37 mm diameter, 0.8-micron pore size mixed-cellulose ester filters in plastic cassettes to trap particulates and a 150 mg Chromosorb 102 adsorbent tube to trap vapors. Urine samples were collected to estimate the excretion of absorbed dose. Participants were instructed to collect all urine voided on the day preceding spraying, the day of spraying and for three consecutive days post spray application.

All workers wore pre-laundered one-piece, long-sleeved, front zippered coveralls (65% polyester, 35% cotton). The coveralls were worn over the applicators' street clothes which typically included denim jeans and either a cotton T-shirt, sleeveless top, or a long-sleeved flannel shirt. Workers wore gauntlet-style neoprene rubber gloves during a mixing/loading activity. During the spray application, most workers wore fitted wrist-length vinyl-dipped cotton gloves. Some operators used neoprene rubber gloves during spraying. Some workers also wore dual cartridge, half-face respirators equipped with organic vapor/acid gas cartridges.

The average recoveries of field-spiked samples were 39% for Chromosorb 102 tubes, 19% for membrane filters, 57% for cloth patches, and 78% for hand rinse solution. U.S. EPA (1987) recommends total recovery from field-spiked samples of 50% or greater; whereas, we recommend a recovery rate of 85% or greater for lab studies. Results of the exposure monitoring study were corrected for these field recoveries. Urinary triclopyr was not corrected because field-spiked recoveries for urine samples were close to 100%. The result of clothing penetration evaluation of triclopyr indicated that the chest and thigh regions had the highest penetration compared to other parts of the body. Values for the thighs reached as high as 79%. Results of this study, including inhalation and dermal exposures, clothing penetration, and estimated dermal absorption, are shown in Tables 1a and 1b. Dermal absorption values for three workers were excluded from the overall calculation of the dermal absorption due to reasons mentioned in footnotes of Table 1b. The average dermal absorption value for nine workers from this study was estimated to be $5.4 \pm 3.9\%$.

<u>Exposure monitoring study of triclopyr (Middendorf, 1995):</u>
The second triclopyr exposure monitoring study was also conducted to determine urinary excretion of triclopyr (Middendorf, 1995). Inhalation, potential dermal (covered skin) and dermal exposures (exposed skin) were also measured. The study was conducted at four sites. The first three sites of study were in the Chattahoochee National Forest of northern Georgia. The fourth site was on the Savannah River Plant property near Aiken, South Carolina. There were a total of 22 applicators who participated in the spray application of a 3% solution of Garlon™ 4 herbicide to vegetation. The height of the brush ranged from two to 12 feet with low to high density. The application equipment was a backpack sprayer equipped with either a piston or diaphragm wand or gunjet. The work time for these workers ranged from 4 to 6.25 hours. The amount of triclopyr applied ranged from 1.2 to 2.2 pounds. Some applicators were involved in handling the concentrate during a mixing/loading activity. Methods for monitoring the exposures were similar to the study conducted by Rankin *et al*. (1991).

Results of the study and detailed calculations of the dermal absorption are shown in Tables 2a and 2b. The default clothing penetration of 10% (British Agrochemical Association, 1986) was used as recommended by the author of the report. The reason was that the estimated clothing

penetration from this study was far below a historical value. Also, this default clothing penetration is similar to an average value of 9.7% obtained from the first study. Dermal absorption values of eight applicators were not included in the overall average of this study for various reasons described in the footnotes of Table 2b. The average dermal absorption for 14 applicators was 4.4 ± 3.8%.

The overall average dermal absorption value from the two studies (n = 23) was 4.8 ± 3.8% (Table 3). The average is considerably higher than that obtained from a study in human volunteers (Carmichael *et al*., 1988, 1989).

Recommendation:

An average dermal absorption value of 4.8% is appropriate to be used in the determination of absorbed dosages of triclopyr. The dermal absorption will be reevaluated if the registrant elects to conduct a new human dermal absorption study. We recommend the use of radiolabeled triclopyr and an administered dose similar to field exposure levels.

References:

British Agrochemical Association, Scientific Subcommittee. 1986. Estimation of exposure and absorption of pesticides by spray operators.

Carmichael, N. G., Perkins, J., Nolan, R. J., Flethcher, A. P., Davies, R., Brown, P. M., and Warrington, S. J. 1988. Human dermal absorption study of Garlon™ 4 (A herbicide). DPR. Pesticide Registration Document Number 417-057, ID Number SBRA-110028-E, Record Number 67665.

Carmichael, N. G., Nolan, R. J., Perkins, J. M., Davies, R., and Warrington, S. J. 1989. Oral and dermal pharmacokinetics of triclopyr in human volunteers. *Human Toxicology*. 8: 431-437.

Middendorf, P. J. 1995. Forest worker exposures to triclopyr (3,5,6-tricloro-2-pyridinyloxyacetic acid), butoxyethyl ester during directed foliage applications of Garlon™ 4 herbicide. DPR. Pesticide Registration Document Number 51566-039, ID Number 154699-E, Record Number 138902.

Rankin, M. G., Nolan, R. J., Scortichini, B. H., Davies, D. B., Chen, W. L., Mackay, T. S., Rick, D. L., and Kropscott, B. E. 1991. Evaluation of occupational exposures to triclopyr during mixing, loading and spray application of Garlon™ 4 herbicide to foliage of brush on industrial rights-of-way. DPR. Pesticide Registration Document Number 417-112, ID Number 159680-E, Record Number 145158.

Rech, C. 1988. Garlon™ 4 herbicide: Human pharmacokinetics - oral and dermal absorption studies. A memorandum to M. Black dated August 10. WH&S, DPR.

cc: Sue Edmiston
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Rich Bireley

(TCW/Dermal/Triclop1)

Dermal Absorption of Triclopyr in Humans

(TXL/Dermal/triclop1)

Table 1a. Estimated dermal absorption of triclopyr in humans (Rankin et al., 1991; Doc. No. 417-112; Org # GHS-C-57).

n = 12

	Triclopyr (mg)									
Volunteer	Highest amount in urine	Inhalation exposure	Absorbed inhal. dose (1)	Absorbed dermal dose (2)	Dermal exposure (3)	Potential dermal exposure (4)	% Clothing penetration	Dermal exposure (5)	Total dermal exposure (6)	% Dermal absorption (7)
JW	2.198	0.190	0.095	2.103	12.20	1007	34.0	34.24	46.44	4.5
TV	0.763	0.190	0.095	0.668	5.80	1367	3.3	4.51	10.31	6.5
MM	0.132	0.067	0.034	0.099	0.50	482	25.0	12.05	12.55	0.8
EP	0.259	0.024	0.012	0.247	3.70	532	1.0	0.53	4.23	5.8
AT	8.779	0.710	0.355	8.424	29.50	1583	1.4	2.22	31.72	26.6
MC	0.220	0.250	0.125	0.095	0.60	590	12.0	7.08	7.68	1.2
PM	0.048	0.038	0.019	0.029	2.00	108	4.1	0.44	2.44	1.2
HS	0.301	0.030	0.015	0.286	2.30	12	29.0	0.35	2.65	10.8
DJ	0.730	0.140	0.070	0.660	5.00	108	1.2	0.13	5.13	12.9
LD	0.027	0.023	0.012	0.016	0.30	6.8	1.0	0.01	0.31	5.1
GK	0.642	0.220	0.110	0.532	7.00	1007	1.9	1.91	8.91	6.0
PT	0.501	0.480	0.240	0.261	1.40	324	3.0	0.97	2.37	11.0
						Average	9.7			Average 7.7
	n = replicate									STDEV 7.1

(1) absorbed inhalation dose was calculated based on 50% inhalation uptake and 100% inhalation absorption.
(2) absorbed dermal dose = highest amount in urine - absorbed inhalation dose.
(3) dermal exposure = surface deposition on face and neck, plus hand washes (exposed skin).
(4) potential dermal exposure = surface deposition on clothed body regions (chest, back, arms, legs).
(5) dermal exposure = potential dermal exposure x clothing penetration (coveralls) x 10% (default) clothing penetration for street clothes (worn under coveralls) and covered skin. Street clothes consisted of denim
jeans and a cotton T-shirt, sleeveless top, or a long-sleeved flannel shirt.
(6) total dermal exposure = dermal exposure of exposed skin + dermal exposure of covered skin.
(7) % dermal absorption = absorbed dermal dose (2) x 100/total dermal exposure (6).

Table 1b. Estimated dermal absorption of triclopyr in humans (Rankin et al., 1991; Doc. No. 417-112; Org # GHS-C-57).

n = 9 (not included JW, DJ, and AT)

	Triclopyr (mg)									
Volunteer	Highest amount in urine	Inhalation exposure	Absorbed inhal. dose (1)	Absorbed dermal dose (2)	Dermal exposure (3)	Potential dermal exposure (4)	% Clothing penetration	Dermal exposure (5)	Total dermal exposure (6)	% Dermal absorption (7)
TV	0.763	0.190	0.095	0.668	5.8	1367	3.3	4.51	10.31	6.5
MM	0.132	0.067	0.034	0.099	0.5	482	25.0	12.05	12.55	0.8
EP	0.259	0.024	0.012	0.247	3.7	532	1.0	0.53	4.23	5.8
MC	0.220	0.250	0.125	0.095	0.6	590	12.0	7.08	7.68	1.2
PM	0.048	0.038	0.019	0.029	2.0	108	4.1	0.44	2.44	1.2
HS	0.301	0.030	0.015	0.286	2.3	12	29.0	0.35	2.65	10.8
LD	0.027	0.023	0.012	0.016	0.3	6.8	1.0	0.01	0.31	5.1
GK	0.642	0.220	0.110	0.532	7.0	1007	1.9	1.91	8.91	6.0
PT	0.501	0.480	0.240	0.261	1.4	324	3.0	0.97	2.37	11.0
						Average	8.9		Average	5.4
									STDEV	3.9

(1) absorbed inhalation dose was calculated based on 50% inhalation uptake and 100% inhalation absorption.
(2) absorbed dermal dose = highest amount in urine - absorbed inhalation dose.
(3) dermal exposure = surface deposition on face and neck, plus hand washes (exposed skin).
(4) potential dermal exposure = surface deposition on clothed body regions (chest, back, arms, legs).
(5) dermal exposure = potential dermal exposure x clothing penetration (coveralls) x 10% (default) clothing penetration for street clothes (worn under coveralls) (covered skin). Street clothes consisted of denim jeans and a cotton T-shirt, sleeveless top, or a long-sleeved flannel shirt.
(6) total dermal exposure = dermal exposure of exposed skin + dermal exposure of covered skin.
(7) % dermal absorption = absorbed dermal dose (2) x 100/total dermal exposure (6).

Notes: Estimated dermal absorption rates for JW, DJ, AT were not included in the average because of some unexpected exposure situations observed during the study. JW was probably exposed to triclopyr during the post spray. DJ had a large non dermal component to the exposure which was determined from the difference in the amount of triclopyr calculated by the kinetic model and the urinary factor. In the case of AT, the absorbed dose derived from urinalysis exceeded the personal monitoring estimate by almost six-fold.

Table 2a. Estimated dermal absorption of triclopyr in humans (Middendorf, 1995; Doc. No. 51566-039).

n = 22		Triclopyr-BEE (mg)							
Volunteer	Est. abs. dermal dose of triclopyr (kinetic, mg)	Estimated abs. dermal dose triclopyr-BEE(1)	Dermal exposure (expos. skin) (2)	Potential dermal exposure (cover. skin) (3)	Default % clothing penetration (4)	Dermal exposure (cover. skin) (5)	Total dermal exposure (6)		% Dermal absorption (7)
Site 1									
WT	0.537	0.746	2.100	457	10	45.7	47.800		1.6
MH	0.478	0.664	0.352	205	10	20.5	20.852		3.2
JF	0.207	0.288	0.385	134	10	13.4	13.785		2.1
JDA	0.526	0.731	0.294	168	10	16.8	17.094		4.3
CWH	1.319	1.833	2.200	730	10	73.0	75.200		2.4
Site 2									
MEC	0.750	1.043	2.430	618	10	61.8	64.230		1.6
TRH	0.784	1.090	1.040	196	10	19.6	20.640		5.3
RVA	1.442	2.004	6.240	929	10	92.9	99.140		2.0
LJK	5.071	7.049	4.660	312	10	31.2	35.860		19.7
WHS	0.220	0.306	3.930	122	10	12.2	16.130		1.9
SGG	1.722	2.394	1.500	353	10	35.3	36.800		6.5
Site 3									
NM	6.210	8.632	7.180	871	10	87.1	94.280		9.2
RR	1.980	2.752	2.530	151	10	15.1	17.630		15.6
RH	1.122	1.560	2.950	395	10	39.5	42.450		3.7
MD	0.579	0.805	2.390	112	10	11.2	13.590		5.9
JJ	9.663	13.432	1096.000	6415	10	641.5	1737.500		0.8
Site 4									
G	0.324	0.450	2.180	126	10	12.6	14.780		3.0
H	1.459	2.028	4.720	299	10	29.9	34.620		5.9
I	1.083	1.505	1.340	319	10	31.9	33.240		4.5
J	0.267	0.371	0.459	143	10	14.3	14.759		2.5
K	0.474	0.659	0.185	80	10	8.0	8.185		8.0
L	1.799	2.501	0.476	93	10	9.3	9.776		25.6
Average								Average	6.1
								STDEV	6.3

(1) triclopyr-BEE = triclopyr (acid) x 1.39. Absorbed dose for "J" was from the urinary triclopyr because it could not be modeled.
(2) dermal exposure (exposed skin) = surface deposition on face and neck, plus hand washes (exposed skin).
(3) potential dermal exposure (covered skin) = surface deposition on clothed body regions (chest, back, arms, legs).
(4) default clothing penetration of 10% is similar to an average value reported in Rankin et al. (1991).
(5) dermal exposure (covered skin) = potential dermal exposure x clothing penetration factor.
(6) total dermal exposure = dermal exposure of exposed skin + dermal exposure of covered skin.
(7) % dermal absorption = absorbed dermal dose (1) x 100/total dermal exposure (6).

Table 2b. Estimated dermal absorption of triclopyr in humans (Middendorf, 1995; Doc. No. 51566-039).

n = 14 (not included CWH, LJK, SGG, MD, JJ, I, K, and L)

		Triclopyr-BEE (mg)						
Volunteer	Est. abs. dermal dose of triclopyr (kinetic, mg)	Estimated abs. dermal dose triclopyr-BEE(1)	Dermal exposure (expos. skin) (2)	Potential dermal exposure (cover. skin) (3)	Default % clothing penetration (4)	Dermal exposure (cover. skin) (5)	Total dermal exposure (6)	% Dermal absorption (7)
Site 1								
WT	0.537	0.746	2.100	457	10	45.7	47.8	1.6
MH	0.478	0.664	0.352	205	10	20.5	20.9	3.2
JF	0.207	0.288	0.385	134	10	13.4	13.8	2.1
JDA	0.526	0.731	0.294	168	10	16.8	17.1	4.3
Site 2								
MEC	0.750	1.043	2.430	618	10	61.8	64.2	1.6
TRH	0.784	1.090	1.040	196	10	19.6	20.6	5.3
RVA	1.442	2.004	6.240	929	10	92.9	99.1	2.0
WHS	0.220	0.306	3.930	122	10	12.2	16.1	1.9
Site 3								
NM	6.210	8.632	7.180	871	10	87.1	94.3	9.2
RR	1.980	2.752	2.530	151	10	15.1	17.6	15.6
RH	1.122	1.560	2.950	395	10	39.5	42.5	3.7
Site 4								
G	0.324	0.450	2.180	126	10	12.6	14.8	3.0
H	1.459	2.028	4.720	299	10	29.9	34.6	5.9
J	0.267	0.371	0.459	143	10	14.3	14.8	2.5
Average							Average	4.4
							STDEV	3.8

(1) triclopyr-BEE = triclopyr (acid) x 1.39. Absorbed dose for "J" was from the urinary triclopyr because it could not be modeled.
(2) dermal exposure (exposed skin) = surface deposition on face and neck, plus hand washes (exposed skin).
(3) potential dermal exposure (covered skin) = surface deposition on clothed body regions (chest, back, arms, legs).
(4) default clothing penetration of 10% is similar to an average value reported in Rankin et al. (1991).
(5) dermal exposure (covered skin) = potential dermal exposure x clothing penetration factor.
(6) total dermal exposure = dermal exposure of exposed skin + dermal exposure of covered skin.
(7) % dermal absorption = absorbed dermal dose (1) x 100/total dermal exposure (6).

Notes: CWH, LJK, SGG, MD, JJ, I, and K had significant exposure to triclopyr during the post spraying interval. Dermal absorption rates for these applicators were not used for the calculation of the average. A dermal absorption value of 25.6% for L was also excluded because it was determined as a statistical outlier, i.e., > 5 SDs (or > 99.99th percentile value) from the mean calculated without the outlier.

Table 3. Average dermal absorption from two studies (Rankin et al., 1991 (GHS-C-57) and Middendorf, 1995).

n = 23

Dermal absorption (%)			
Rankin et al. (1991)			Middendorf, 1995
TV	6.5	1.6	WT
MM	0.8	3.2	MH
EP	5.8	2.1	JF
MC	1.2	4.3	JDA
PM	1.2	1.6	MEC
HS	10.8	5.3	TRH
LD	5.1	2.0	RVA
GK	6.0	1.9	WHS
PT	11.0	9.2	NM
		15.6	RR
		3.7	RH
		3.0	G
		5.9	H
		2.5	J
Average	4.8		
STDEV	3.8		