DATA EVALUATION RECORD

CHLOROTHALONIL

Study Type: §85-1; Metabolism Study in Dogs

Work Assignment No. 3-01-91 E (MRID 45710217)

Prepared for
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Arlington, VA 22202

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DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Dog

PC CODE: 081901 **DP BARCODE:** D301496

TEST MATERIAL (RADIOCHEMICAL PURITY): [Phenyl-U-^{14}C]-Chlorothalonil (>97%)

SYNONYM: 2,4,5,6-tetrachloro-1,3-benzenedicarbonitrile; tetrachloroisophthalonitrile;

CITATION: Aikens, P.J. (1997) Chlorothalonil: metabolism in the dog. Huntingdon Life Sciences, Ltd., Huntingdon, Cambridgeshire, England. Laboratory Study ID: VCM 65/963758, April 25, 1997. MRID 45710217. Unpublished.

SPONSOR: Vischim S.r.l., Via Friuli, Cesano Maderno, Milan, Italy

EXECUTIVE SUMMARY: In a dog metabolism study (MRID 45710217), [Phenyl-U-^{14}C]-Chlorothalonil (Batch # 1021; radiochemical purity >97%) in 1.0% (w/v) aqueous sodium carboxymethylcellulose was administered to male beagle dogs by gavage. A single dose of the compound was administered to three dogs at 1.5 mg/kg nominal in an excretion balance/plasma pharmacokinetics study and a tissue distribution/metabolite profile study. Metabolites were quantified and identified in urine and feces from the excretion balance/plasma pharmacokinetics study, and in bile, blood, liver, and kidney from the tissue distribution/metabolite profile study. The purpose of this study was to evaluate the differences in the metabolism of Chlorothalonil by comparing data generated in the dog to similar data generated in a rat metabolism study (MRID 45710216).

After 120 h, total recovery was 93.2% of the administered dose. The test compound was readily absorbed, as radioactivity was detected in both plasma and whole blood at 0.25 h (first time point analyzed). A mean maximum plasma concentration was observed after six h, with a calculated half life of 74.2 h. The majority of the radioactivity was recovered in the feces with most recovery occurring in the first 24 h. Approximately one-half of the administered dose was extracted from the feces collected from 0-48 h. Urine accounted for a smaller percentage of the dose with the majority of radioactivity recovered in the first 24 h. The majority of radioactivity was accounted for in both excreta during the first 48 h. Cage wash accounted for an additional 1.26% of the dose.

The test compound was not extensively retained by any tissue. The dogs were individually sacrificed at 6, 12, and 48 h, and it was stated that these times were based on the time of peak

plasma concentration, half peak plasma concentration, and a terminal time. Blood, plasma, liver, and bile all demonstrated maximal concentrations at 6 h, decreasing substantially by 48 h. However, radioactivity in the kidney decreased at a much slower rate out to 48 h.

HPLC analysis of urine, bile, and feces revealed extensive metabolism of the test compound in all matrices. Parent was present in the fecal extracts at 19.1% of the administered dose. Parent was not present in the urine, and no fraction accounted for >0.5% of the administered dose in urine. There were four major urinary radioactive fractions accounting for a total of 1.2% of the administered dose; one fraction was identified as the diglutathione conjugate by co-chromatography. Analysis following treatment of urine with β-glucuronidase/sulphatase showed no evidence of deconjugation. Pools of liver, kidney, and plasma were extracted and analyzed by HPLC. In the liver extracts, two major components were identified as the diglutathione and triglutathione conjugates. In the kidney extracts, at least eight major components were observed, with monoglutathione, diglutathione, triglutathione, and dicysteine conjugates identified. The dicysteine conjugate was also identified in plasma extracts.

In summary, when male dogs are compared to male rats, a number of broad similarities may be seen, including low absorption of the administered dose and rapid metabolism and excretion. The metabolite profiles of the urine, bile, and tissue extracts show differences in the presence and proportions of the metabolites present, most notably the presence of mercapturic acid-containing moieties in the rat that were not detected in the dog.

This study is classified **acceptable/non-guideline** and does not satisfy the guideline requirements for a metabolism study in the dog [OPPTS 870.7485/OECD 417].

COMPLIANCE: Signed and dated Data Confidentiality, GLP compliance, and Quality Assurance statements were provided.

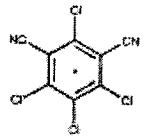
I. MATERIALS AND METHODS

A. MATERIALS

1. Test compound:

Radiolabeled test material 1: [Phenyl-U-^{14}C]-Chlorothalonil

Radiochemical purity:	>97% (determined by TLC)
Specific Activity:	47.5 mCi/mmol (178.6 µCi/mg)
Batch No.:	1021
Structure:	



(position of ^{14}C-label indicated by *)

Non-radiolabeled test material 1: Chlorothalonil

Description:	White crystalline solid
Batch No.:	14/09/93/1
Purity:	99.8%
CAS # of TGAI:	1897-45-6

Non-radiolabeled test material 2:

Batch No.:	25
Purity:	99.18%

2. Vehicle: 1.0% (w/v) aqueous sodium carboxymethylcellulose solution

3. Test animals:

Species:	Dog	
Strain:	Beagle	
Age and weight at dosing:	9-10 months; 13.3-15.1 kg	
Source:	Interfauna (no other information provided)	
Housing:	Dogs were individually housed in metabolism cages	
Diet:	SQC lab diet A (Biosure Ltd., Witham, Essex, UK), *ad libitum*, except for a period of approximately 16h prior to and 4 h following dosing	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	21±3°C
	Humidity:	40-70%
	Air changes:	Approximately 15/h
	Photoperiod:	12 h light/dark
Acclimation period:	Approximately 3 weeks	

4. Purpose: The purpose of this study was to evaluate the differences in the metabolism of Chlorothalonil by comparing data generated in the dog to similar data generated in a rat metabolism study (MRID 45710216).

5. Preparation of dosing solutions: A stock solution (designated VCM 66-1) was prepared by dissolving the radiolabeled test substance in acetonitrile. A measured volume of VCM 66-1 was

225

mixed with non-radioactive Chlorothalonil to make a stock formulation (designated VCM 66-2) that was used for the preparation of the dosing solution used in the excretion balance/plasma pharmacokinetics study. The specific activity of VCM 66-2 was 33 µCi/mg (determined by HPLC). A second stock formulation (designated VCM 65-4) was prepared by purifying an aliquot of VCM 66-1 by preparative TLC and mixing this product with a measured volume of VCM 66-2. This formulation was used to prepare the dosing solution used in the tissue distribution/metabolite profile study. The specific activity of VCM 65-4 was 39.9 µCi/mg. To make the dosing solutions, an appropriate volume of VCM 66-2 or VCM 65-4 was concentrated to dryness under nitrogen, and then resuspended in a calibrated volume of 1.0% (w/v) aqueous carboxymethylcellulose vehicle by sonication and using a drill-mounted Teflon pestle.

No information was provided concerning the stability of the formulations. However, it was stated that doses were administered within two h of preparation. Triplicate aliquots of the prepared dosing solutions were analyzed by liquid scintillation counting (LSC) to confirm concentration and homogeneity. The radiochemical purity of all stock and dose suspensions was >97% (determined by TLC). The specific activities of the formulations were 73,249 dpm/µg for the excretion balance/plasma pharmacokinetics study and 88500 dpm/µg for the tissue distribution/metabolite profile study.

B. STUDY DESIGN AND METHODS

1. Group arrangements: Animals were assigned to the test groups presented in Table 1. The dose level of 1.5 mg/kg was chosen to be comparable with the low dose used in the rat metabolism study (MRID 45710216). Animals were weighed on the day of dosing.

Table 1. Study groups for [^{14}C]-Chlorothalonil metabolism study in dogs[a]

Nominal dose (mg/kg)	Mean actual dose (mg/kg)	# animals/ group	Comments
Excretion Balance/Plasma Pharmacokinetics Study			
1.5	1.00	3 males	Feces were collected daily for five days; urine was collected at 0-6 and 6-24 h, then daily for five days. Cage washes were collected daily after excreta collection. Blood samples were taken prior to dosing and at regular intervals post-dosing.
Tissue Distribution/Metabolite Profile Study			
1.5	1.24	3 males	Animals were killed at 6, 12, and 48 h, and blood, bile, kidneys, and liver were collected. Pooled urine and feces from the previous study and blood, bile, kidneys, and liver were analyzed for metabolites.

a Data were obtained from page 21 and Appendix 1 on page 78 of the study report.

2. Dosing and sample collection: Animals were dosed by oral gavage with dose amounts based on individual body weights. A nominal dose volume of 0.6 mL/kg was used. The dose suspension was dispensed by weight into individual pre-weighed syringes, and administered to their respective animal via an individual gavage tube. A small quantity of either distilled water or vehicle was used to rinse the dose into the dogs. The dogs were fasted 16 h prior to dosing and 4 h following dosing. The administered doses approximated the nominal doses. The actual mean administered doses and the number of animals treated in each study are reported in Table 1.

a. Pharmacokinetic studies: All studies were performed with single oral doses of the test compound.

i. Excretion balance/plasma pharmacokinetic study: Dogs were dosed once with 1.5 mg/kg of the radiolabeled test compound and housed in metabolism cages. Urine samples were collected in dry ice-cooled receivers at 0-6 and 6-24 h and then at daily intervals up to five days post-dosing. Feces were collected at daily intervals for up to five days post-dosing. Cage washes were collected daily after excreta were collected. Blood samples were taken immediately prior to dosing and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 120 h post-dosing.

ii. Tissue distribution/metabolite profile study: The dogs from the previous study were dosed with 1.5 mg/kg of the radiolabeled test compound approximately four months after the initial dosing. Dogs were killed individually at 6, 12, or 48 h post-dosing by pentobarbitone overdose followed by exsanguination, and liver, kidneys, and samples of blood and bile were taken and analyzed for radioactivity content and metabolites. Pooled urine and feces from the previous study also were analyzed for metabolite content.

iii. Sample preparation and analysis: Fecal samples from the 0-24 h interval of the excretion balance/plasma pharmacokinetics study were extracted once with acetonitrile:ethyl acetate (1:1 v/v), then with acetonitrile only, then five times with acetonitrile:water (1:1 v/v). Fecal samples from the 24-48 h interval were extracted as described above for the first four extractions. Fecal residues and fecal samples from the remaining time points were homogenized with half their mass of water. Individual liver and kidney samples were homogenized with an electric blender. Aliquots of each organ sample were extracted a total of six times: three times with acetonitrile:ethyl acetate (1:1 v/v) and three times with acetonitrile:water (1:1 v/v). Additionally, tissue samples were pooled, concentrated, and extracted with hexane. Plasma samples were extracted with acetone, and a plasma pool was prepared and concentrated.

Radioactivity was measured by liquid scintillation counting (LSC). Liquid samples (urine, bile, cage washes, plasma, and tissue, plasma, and fecal extracts and pools) were mixed with scintillant and counted. Samples of fecal, tissue, and plasma residues, unextracted feces, liver, kidney, and whole blood were combusted in oxygen, trapped, mixed with scintillant and counted. It was stated that radioactivity in amounts less than twice background levels was considered to be below the limit of accurate measurement.

b. Metabolite characterization: The urine, bile, fecal extracts, plasma, liver, and kidney were analyzed by HPLC and/or TLC to determine the metabolite profiles.

Urine samples from the excretion balance/plasma pharmacokinetic studies collected during 0-6 and 6-24 h were combined into a single representative pool and analyzed. Samples were acidified to pH 5.0 with sodium acetate buffer. β-Glucuronidase/sulfatase was added to an aliquot of the acidified urine, and to a positive control acidified urine sample containing enzyme and phenolphthalein glucuronide. Enzyme-treated urine samples were incubated overnight at 37°C. Additionally, acidified and intact urine samples were incubated overnight either at ambient temperature or at 37°C. At the end of the incubation period, the enzyme-treated sample

was tested to ensure the enzyme was still active. Aliquots of these urine samples were analyzed by HPLC, and selected samples were analyzed by TLC.

A single representative fecal extract pool of the 0-24 and 24-48 h extracts was prepared, and the volume reduced with a rotary evaporator. This concentrate was made up to volume with acetonitrile:water (1:1 v/v). Samples were analyzed by HPLC and TLC.

Plasma extracts were analyzed by HPLC and TLC. Co-chromatography was performed with selected reference standards. The aqueous phase of the hexane extracts of the liver and kidney pools was analyzed by HPLC; the concentrated hexane samples were analyzed by TLC. Bile samples were analyzed by HPLC and TLC.

3. **Statistics:** Statistical analyses were limited to calculations of mean and standard deviation.

II. RESULTS

A. PHARMACOKINETIC STUDIES

1. **Excretion balance/plasma pharmacokinetics study:** After 120 h, total recovery (Table 2a) was 93.2% of the administered dose. The majority of the radioactivity was recovered in the feces (88.6% of the administered dose) with most recovery occurring in the first 24 h (86.7%). Approximately 53.4% of the administered dose was extracted from the feces collected from 0-48 h; 34.7% of the dose was unextractable. Urine accounted for a smaller percentage of the dose (3.36%); again, the majority of radioactivity was recovered in the first 24 h (3.12%). The majority of radioactivity was accounted for in both excreta during the first 48 h. Cage wash accounted for an additional 1.26% of the dose.

Table 2a. Mean (±SD) recovery of radioactivity excreted following a single 1.5 mg/kg oral dose of [^{14}C]-Chlorothalonil in dogs[a]

Matrix		% Administered Dose
Urine	0-6 h	1.44±0.20
	6-24 h	1.68±0.26
	24-48 h	0.14±0.05
	48-120 h[b]	0.10
Total urine		3.36±0.12
Feces	0-24 h	86.7±10.9
	24-48 h	1.43±0.98
	48-120 h[b]	0.45
Total feces		88.6±10.2
Cage wash		1.26±0.39
Total recovery		93.2±9.78

a Data were obtained from Table 2 on page 39 of the study report; data are the mean of three dogs.
b Calculated by reviewers by adding values for intervals between 48 and 120 h for each dog and then averaging.

The test compound was readily absorbed, as radioactivity was detected in both plasma and whole blood at 0.25 h (first time point analyzed). A mean maximum plasma concentration (C_{max}) of 0.25 µg equivalents/mL was observed after six h (T_{max}). The half life ($t_{½}$) was calculated to be 74.2 h and the AUC was 6.3 µg equivalents•h/mL (Table 2b). It was stated that the elimination constant, $t_{½}$, and AUC were estimates since the measurement period for the elimination constant was less than twice the estimated $t_{½}$, and the extrapolated area of the AUC was >20% of the AUC_{120}.

Table 2b. Mean plasma pharmacokinetic parameters for radioactivity following a single 1.5 mg/kg oral dose of [^{14}C]-Chlorothalonil in dogs[a]

Parameter	Results
C_{max} (µg equivalents/mL)[b]	0.248±0.065
T_{max} (h)	6.0
AUC_{120} (µg equivalents•h/mL)	4.7±1.0
AUC (µg equivalents•h/mL)	6.3±1.6
k_{el} (h^{-1})	0.0093±0.0016
$t_{½}$ (h)	74.2

a Data were obtained from Table 4 on page 41 of the study report; data are the mean of three dogs.

2. <u>Tissue distribution/metabolite profile study</u>: The test compound was not extensively retained by any tissue (Table 3). The dogs were individually sacrificed at 6, 12, and 48 h, and it was stated that these times were based on the time of peak plasma concentration, half peak plasma concentration, and a terminal time. Blood, plasma, liver, and bile all demonstrated maximal concentrations at 6 h, decreasing substantially by 48 h. However, kidney had a concentration of 0.37 µg equivalents/g at 6 h, decreasing to 0.36 µg equivalents/g at 12 h and remaining at 0.15 µg equivalents/g at 48 h.

Table 3. Mean concentrations of radioactivity in selected tissues of dogs following a single oral dose of [^{14}C]-Chlorothalonil[a]

Sacrifice time (h)	µg equivalents/g				% administered dose
	Blood	Plasma	Liver	Kidney	Bile
6	0.207	0.458	0.654	0.365	2.7
12	0.135	0.274	0.480	0.360	1.0
48	0.013	0.026	0.034	0.154	0.05

a Data were obtained from Table 9 on page 46 of the study report; data are from individual dogs.

B. METABOLITE CHARACTERIZATION STUDIES: HPLC analysis of urine, bile, and feces revealed extensive metabolism of the test compound in all matrices. Parent was present in the fecal extracts at 19.1% of the administered dose. Parent was not present in the urine, and no fraction accounted for >0.5% of the administered dose in urine. In the urine, there were four major radioactive fractions accounting for a total of 1.2% of the administered dose; one fraction accounting for 0.30% was identified as the diglutathione conjugate by co-chromatography. Analysis following treatment of urine with β-glucuronidase/sulphatase showed no evidence of deconjugation. One biliary metabolite fraction accounted for 0.63% of the administered dose at 6 h and 23.4% of the total biliary radioactivity; however, this fraction was not identified due to matrix effects.

Pools of liver, kidney, and plasma were extracted and analyzed by HPLC. The extracts represented mean values for 6 and 12 h of 72.4% of the liver radioactivity and 58.9% of the kidney radioactivity. The mean amount of radioactivity extracted from the plasma at all three time points was 87.6%. In the liver extracts, two major components were identified as the diglutathione (28.8% of the aqueous soluble liver extract at 6 h) and triglutathione (25.9%) conjugates. In the kidney extracts, at least eight major components were observed, with monoglutathione (8.7% of the aqueous soluble kidney extract at 6 h), diglutathione (12.8%), triglutathione (7.8%), and dicysteine (7.8%) conjugates identified. The dicysteine conjugate was also identified in plasma extracts.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The absorption of Chlorothalonil in dogs after an oral dose is low and the metabolism of the absorbed dose is rapid. The primary route of elimination of the radiolabel was the feces, although a small amount of the radiolabel was excreted in the urine. The clearance of the majority of the radiolabel was complete within 24 h after dosing. Plasma pharmacokinetic analysis confirmed these observations and indicated that peak plasma concentrations were reached at 6 h and the half-life of the radiolabel in plasma was 74.2 h. Metabolism of the absorbed radioactivity was extensive and rapid. No unchanged Chlorothalonil was detected in the urine; a major radioactive urinary metabolite which represented 0.3% of the administered dose was identified as the diglutathione conjugate of Chlorothalonil. Chlorothalonil was the major component of the fecal extracts. All other urinary and fecal metabolites were present at <0.5% of the administered dose. Diglutathione and triglutathione conjugates of Chlorothalonil were two of the major liver metabolites. These were

230

also found in kidney along with monoglutathione and dicysteine conjugates. Bile was demonstrated to have one major unidentified metabolite.

B. REVIEWER COMMENTS: After 120 h, total recovery was 93.2% of the administered dose. The majority of the radioactivity was recovered in the feces (88.6% of the administered dose) with most recovery occurring in the first 24 h (86.7%). Approximately 53.4% of the administered dose was extracted from the feces collected from 0-48 h; 34.7% of the dose was unextractable. Urine accounted for a smaller percentage of the dose (3.36%); again, the majority of radioactivity was recovered in the first 24 h (3.12%). The majority of radioactivity was accounted for in both excreta during the first 48 h. Cage wash accounted for an additional 1.26% of the dose.

The test compound was readily absorbed, as radioactivity was detected in both plasma and whole blood at 0.25 h (first time point analyzed). A mean maximum plasma concentration (C_{max}) of 0.25 µg equivalents/mL was observed after six h (T_{max}). The half life ($t_{½}$) was calculated to be 74.2 h and the AUC was 6.3 µg equivalents•h/mL. It was stated that the elimination constant, $t_{½}$, and AUC were estimates since the measurement period for the elimination constant was less than twice the estimated $t_{½}$, and the extrapolated area of the AUC was >20% of the AUC_{120}.

The test compound was not extensively retained by any tissue. The dogs were individually sacrificed at 6, 12, and 48 h. Blood, plasma, liver, and bile all demonstrated maximal concentrations at 6 h, decreasing substantially by 48 h. However, kidney had a concentration of 0.37 µg equivalents/g at 6 h, decreasing to 0.36 µg equivalents/g at 12 h and remaining at 0.15 µg equivalents/g at 48 h.

HPLC analysis of urine, bile, and feces revealed extensive metabolism of the test compound in all matrices. Parent was present in the fecal extracts at 19.1% of the administered dose. Parent was not present in the urine. No fraction accounted for >0.5% of the administered dose in urine. There were four major urinary radioactive fractions accounting for a total of 1.2% of the administered dose; one fraction accounting for 0.30% was identified as the diglutathione conjugate by co-chromatography. Analysis following treatment of urine with β-glucuronidase/sulphatase showed no evidence of deconjugation. One biliary metabolite fraction accounted for 0.63% of the administered dose at 6 h and 23.4% of the total biliary radioactivity; however, this fraction was not identified due to matrix effects.

Pools of liver, kidney, and plasma were extracted and analyzed by HPLC. The extracts represented mean values for 6 and 12 h of 72.4% of the liver radioactivity and 58.9% of the kidney radioactivity. The mean amount of radioactivity extracted from the plasma at all three time points was 87.6%. In the liver extracts, two major components were identified as the diglutathione and triglutathione conjugates, accounting for 26-29% of the aqueous soluble liver extract at 6 h. In the kidney extracts, at least eight major components were observed, with monoglutathione, diglutathione, triglutathione, and dicysteine conjugates identified and accounting for 7.8-12.8% of the aqueous soluble kidney extract at 6 h. The dicysteine conjugate was also identified in plasma extracts.

The purpose of this study was to evaluate the differences in the metabolism of Chlorothalonil by comparing data generated in the dog to similar data generated in a rat metabolism study (MRID 45710216). When male dogs are compared to male rats, a number of broad similarities may be seen, including low absorption of the administered dose and rapid metabolism and excretion. The metabolite profiles of the urine, bile, and tissue extracts show differences in the presence and proportions of the metabolites present, most notably the presence of mercapturic acid-containing moieties in the rat that were not detected in the dog.

This metabolism study in the dog is classified **acceptable/non-guideline**.

C. **STUDY DEFICIENCIES:** The following deficiencies were noted but do not change the outcome of this review:

- Single dogs were used for each time point of the tissue distribution/metabolite profile study. Tier 1 data requirements state a minimum of four young adult male animals are required.

- The same three dogs were used for both studies; however, since an interval of approximately four months passed between dosings, and only a single 1.5 mg/kg dose was administered, this was not expected to influence the experimental outcomes.

ATTACHMENT

Pages 12-16 of the study report
(MRID 45710217)

Chlorothalonil DER (MRID# 45710217)

Page _____ is not included in this copy.

Pages 13 through 17 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

__ X___ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

_____ Proprietary information pertaining to the chemical composition of an inert ingredient provided by the source of the ingredient.

_____ Attorney-Client Privilege.

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