UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

APR 2 8 1993

MEMORANDUM

SUBJECT: EPA ID 018301; Chlorpropham; Review of the Metabolism Study (85-1) (MRID# 420069-01) by Clements International Corp.

Shaughnessy No.: 018301.
Tox.Chem. No.: 510A.
Cas No.: 2239-92-1.
DP Barcode: D168846.
Case: 818637.
Submission No.: S402750.

From: David G Anderson, PhD *David G Anderson 10/5/92*
Section 3
Toxicology Branch-1
Health Effects Division (H7509C)

To: Walter Waldrop/Venus Eagle PM-71
Reregistration Branch
Special Review and
Registration Division (H7508C)

Thru: Karen Hamernik, PhD. *4/23/93*
Acting Section Head
Section 3, Toxicology Branch-1
Health Effects Division (H7509C)

A. CONCLUSIONS:

The applicable data requirements for reregistration of chlorpropham have been determined by HED and transmitted to the registrant. Any further data inadequacies must wait for a committee determination prior to the RED. However, there are major data gaps in the chronic and oncogenicity testing, currently being conducted by the Task Force for Chlorpropham Re-registration.

The report submitted with DP D168846 is acceptable under guideline 85-1 for metabolism of chlorpropham in the rat.

B. ACTION REQUESTED:

Review attached reregistration case. Identify applicable data requirements and note

those data for which adequate data has not been submitted. Comment on the report on the 85-1 study of chlorpropham.

C. BASES FOR THE CONCLUSIONS:

The status of the required data for chlorpropham was reviewed in 1991 by HED and will be reviewed again for a committee prior to writing the RED for chlorpropham sometime in 1994. The major data gaps were addressed in the registration standard for chlorpropham. Chronic and oncogenicity studies are being conducted.

The study submitted with the DP Barcode D168846 was reviewed by Clement International Corp. and conclusions are indicated below.

> Robinson, RA and Liu, David DW, Metabolism of 14C-Chlorpropham in Rats - Definitive FIFRA study, Metabolism Analysis and Quantitation. August 20, 1991. Study No. XBL90051. Report No. RPT0058. MRID# 420069-01.

Chlorpropham was administered by gavage to 5 Sprague Dawley rats per sex per group at 5 mg/kg and 200 mg/kg/day in single doses or multiple doses over 15 days, respectively. A single 0.5 mg/kg IV dose was also administered to other groups of rats.

Chlorpropham was rapidly absorbed and metabolized essentially 100% prior to excretion in the urine with small amounts in feces. Within 24 hours 82-92% of the dose was recovered in the urine and 3-5% in the feces. Peak excretion at the low dose occurred at 4-12 hours (49-62% of the dose) and at the high dose between 8-24 hours (59-64% of the dose). Less than 0.03% of doses were recovered as $[c^{14}]CO_2$ over a 3-day period. The approximate one-half life of chlorpropham in the rat is 8 hours at the low dose and 9 hours for the high dose in males and females. Three major metabolic routes are proposed for chlorpropham; (1) hydroxylation at the 4'-position and conjugation, (2) oxidation of the isopropyl side chain to form isopropanol and isopropinate moieties, and decarbamilation to form 3-chloroaniline, then N-acetylation, (3) 4'-hydroxylation, and conjugation.

Core classification: Minimum. The study is acceptable under Guideline 85-1 for metabolism in the rat.

Cmemo for CIC generated review of metabolism/chlorpropham/420069-01/D168846/HED proj.# 1-2385/B:\CHLORV25.10A\CMMETAB1.092/DANDERSON/10/5/92.*

DOC930008

FINAL

DATA EVALUATION REPORT

CHLORPROPHAM

Study Type: Metabolism

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Author Karen N Gan Date 4/27/92
Karen Gan

Reviewer Sanju Diwan Date 4/27/92
Sanju Diwan

QA/QC Manager Sharon A. Segal Date 4/27/92
Sharon Segal

Contract Number: 68D10075
Work Assignment Number: 1-43
Clement Number: 91-145
Project Officer: James Scott

EPA Reviewer: Dave Anderson, Ph.D. Signature: [signature]
Review Section III, Toxicology Branch I, Date: 10/5/92.
Health Effects Division

Section Head: Henry Spencer, Ph.D. Signature: [signature]
Review Section III, Toxicology Branch I, Date: 4/23/93
Health Effects Division

DATA EVALUATION REPORT

STUDY TYPE: Metabolism

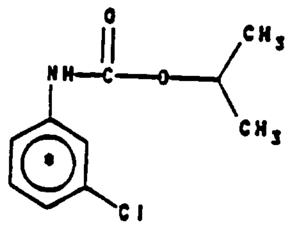
EPA IDENTIFICATION NUMBER: 510A

Tox. Chem. Number:

MRID Number: 420069-01

TEST MATERIAL: Chlorpropham (CASRN 2239-92-1)

SYNONYMS: CIPC; Isopropyl-m-chlorocarbamilate



* denotes the position of the [^{14}C] label

SPONSOR: Chlorpropham Task Force, P.O. Box 301, Liberty, MO 64068

SPONSOR REPRESENTATIVE: Xenobiotic Laboratories, Inc., P.O. Box 3205, Princeton, NJ 08543

TESTING FACILITY: Biological Test Center, P.O. Box 19791, 2525 McGaw Avenue, Irvine, CA 92713-9791

AUTHORS: Robert A. Robinson (Volumes 1 and 2) and Dave D.W. Liu (Volume 1)

TITLE OF REPORT: Metabolism of 14C-Chloropropham in Rats - Definitive FIFRA Study, Metabolism Analysis and Quantitation. Study No. XBL90051. Report No. RPT0058. pp. 1-327 (Volume 1) and pp. 328-615 (Volume 2).

DATE OF REPORT: August 20, 1991

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CONCLUSIONS: The absorption, distribution, metabolism, and excretion of chlorpropham were studied in groups of male and female Sprague-Dawley rats administered a single oral gavage dose of 5 or 200 mg/kg [^{14}C]chlorpropham, or a 14-day repeated oral dosing of 5 mg/kg unlabeled chlorpropham followed by a single dose of 5 mg/kg [^{14}C]chlorpropham on day 15. An additional group of rats received an single intravenous injection of 0.5 mg/kg [^{14}C]chlorpropham.

[^{14}C]Chlorpropham was rapidly absorbed, distributed, metabolized, and excreted in rats for all dosing regimens. The 7-day recoveries were >90% for all dosing groups. Most of the radioactivity was eliminated in the urine (82.28-92.34% of dose) within 24 hours, while recovery in the feces (3.02-5.19%) was low for all dosing groups. The peak excretion of chlorpropham in the urine was 4-12 hours for the low-dose groups (48.90-61.96% of the dose) and 8-24 hours for the high-dose group (59.27-64.14%). ~~level of~~ — The oral absorption rate could not be determined because the blood levels were not measured throughout the study. The preliminary study conducted on rats administered radiolabeled 5, 100, 300, and 500 mg/kg chlorpropham indicated that less than 0.03% of the administered radioactivity was recovered in the expired air as [^{14}C]CO_2 over a 3-day period.

The study indicates that chlorpropham and/or its metabolites do not bioaccumulate following oral or intravenous exposure. The distribution of chlorpropham was minimal; the tissues contained negligible levels of radioactivity with a total recovery of 0.13-0.42% of administered dose in the tissues (including carcass) at postexposure day 7.

The metabolism of chlorpropham is extensive because the unmetabolized parent compound was detected in only some of the fecal samples (<2% of administered dose) and was not detected in any of the urine samples. There were 21 radioactive bands detected in the urine of which 13 were identified as metabolites of chlorpropham. In the feces, 4-6 metabolites were identified. In the preliminary study, the metabolic pattern in the 500-mg/kg group was similar to that observed for the groups in the primary study.

There were no remarkable sex-, dose-, or route-related differences in the absorption, distribution, metabolism, or elimination of [^{14}C]chlorpropham in exposed rats. The study also showed that oral administration of 5 and 200 mg/kg chlorpropham, as well as intravenous dosing with 0.5 mg/kg/day, did not induce any apparent treatment-related clinical effects.

STUDY CLASSIFICATION: The study satisfies the minimum requirements set forth under Guideline 85-1 (and Addendum 7) for a metabolism study in rats and, therefore, is judged to be acceptable.

A. MATERIALS

1. Test Substance

The unlabeled test material (lot number 20629-3-7) was a tan-colored solid provided by Dartec. The test material was purified by Ricerca, Inc., and the purity was determined to be 99.5%.

The radiolabeled chlorpropham (lot number CSL-90-268-70-01) was labeled with [^{14}C] on the aromatic ring. It was provided by Chemsyn Science Laboratories. The labeled preparation had a specific activity of 58.8 mCi/mmol. A radiochemical purity of >98% by HPLC was determined by the Biological Test Center prior to study initiation.

2. Test Animals

Four-to-six-week old male and female Sprague-Dawley rats were obtained from Charles River Laboratories, Wilmington, MA. A single oral gavage dose or repeated dosing of chlorpropham was administered to 5 males and 5 females. An additional group of 10 animals received 0.5 mg/kg chlorpropham by intravenous injection. The control group received the vehicle dose. The group mean weights of male rats ranged from 207 to 228 grams and the group mean weights of female rats ranged from 165 to 172 grams at the time of the radiolabeled dosing of chlorpropham.

B. METHODS

1. Dosing Solutions

The nonlabeled and radiolabeled oral dosing solutions were prepared in corn oil (Mazola). The specific activities of these solutions were 37,831, 38,691, 982, and 611,570 dpm/µg for the single 5-mg/kg, repeated 5-mg/kg, single 200-mg/kg, and intravenous 0.5-mg/kg dosing solutions, respectively. The control group received corn oil. The solutions were administered by oral gavage at 5 mL/kg. The dose amount was determined by weighing the dosing syringe before and after dosing. The nonlabeled solutions were stored at 0-4°C. As reported by the authors, the prior tests had demonstrated that chlorpropham was stable in the corn oil.

The intravenous dose solutions were prepared in 0.9% NaCl (saline) in distilled water. The solution was sonicated for 3 minutes three times, then filtered. The dose volumes were administered at 4 mL/kg.

2. Acclimatization and Dosing

Animals were acclimatized for at least a week before the administration of the test material. Animals were housed individually in cages (type unspecified) before and during the study. Rats received food ad libitum except when food was withheld for 18 hours before and 6 hours after dosing, probably to ensure maximum absorption of the test material. The diet (Purina Rat Chow, Ralston Purina Co., St. Louis, MO)

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and water were given ad libitum throughout the study. No contaminants in the food and water were reported to interfere with the study.

Groups of 10 rats (5/sex) were given a single oral dose of 5 or 200 mg/kg [^{14}C]chlorpropham, or were given an oral dose of 5 mg/kg/day of unlabeled chlorpropham for 14 days followed by a single gavage administration of 5 mg/kg [^{14}C]chlorpropham on day 15. Another group of 10 rats were administered a single injection of 0.5 mg/kg into the jugular vein. The control group consisted of 2 male and 2 female rats that received the orally administered vehicle. Animals were transferred to metabolism cages after dose administration. All animals were observed for 7 days (168 hours) following the administration of the labeled chlorpropham, and then sacrificed.

3. Sample Collection

The urine and feces were collected, over dry ice, from animals at the following intervals: 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours after exposure to the labeled dose of chlorpropham. Urine samples were freeze-trapped to avoid oxidation, evaporation, and bacterial degradation. The metabolism cages were rinsed with distilled water and the washings were collected together with the urine. The fecal samples were pooled, homogenated, and then combusted in a Harvey OX-300 (Harvey Instrument, Hillsdale, NJ). Urine, cage wash, and fecal samples were frozen at -15°C until analysis. Following euthanization of rats by exsanguination at day 7 postexposure, major tissues were weighed, homogenated, if necessary, and combusted similar to the fecal samples. Blood was also collected for analysis. Radioactivity in urine, feces extracts, tissues, blood, and plasma was determined by liquid scintillation counting (LSC) (Beckman LS3801), in duplicate. Statistical analyses were limited to simple expressions of variation (i.e., mean or standard deviation).

4. Metabolite Analysis

For the biotransformation assay, the 24-hour urine and fecal samples were each pooled by dosing regimen and sex. For metabolite analysis, pooled rat urine samples were filtered, counted, and analyzed by high-performance liquid chromatography (HPLC) (Kratos Model 400 Solvent Delivery system; Kratos Model 591 Spectroflow Injector/Mixer). The pooled fecal samples were homogenated, mixed with acetonitrile using a Tekmar Tissumizer, filtered, and analyzed by LSC and HPLC. Chromatographic peaks from the HPLC system were collected and qualitated by thin-layer chromatography (TLC) using silica gel TLC (J.T. Baker, silica gel GF 250 μ, 20 x 20 cm) and developed one-dimensionally with the following solvent systems: (1) 10:90 acetonitrile:toluene and (2) 20:80 ammonium hydroxide:isopropanol. The radioactive bands were identified by comparison to synthetic reference standards provided by the sponsor or Aldrich Chemical Company, Inc. Plates were scanned using an AMBIS Image Scanner. The detection limit was 0.8 cpm/cm^2.

5. Protocol

The study followed the protocol.

C. REPORTED RESULTS

1. Preliminary Study

A 3-day pilot study (Wu 1991; CBI Volume 1, Appendix E) was conducted in 4 groups of 2 male and 2 female rats to establish the extent of excretion via expired air and the excretion pattern of chlorpropham. Following a single oral dose of 5, 100, 300, or 500 mg/kg [^{14}C]chlorpropham, approximately 73-92% of the administered dose was recovered in the urine within 24 hours. The radioactivity in the feces was increased in the higher-dose animals. Less than 0.03% was recovered in the expired CO_2. Therefore, an open test system was used for the primary study.

In addition, metabolite isolation and identification were conducted on the 500-mg/kg rat urine to provide information on the metabolite standards to be used in the primary study, as well as to develop appropriate analytical procedures (Liu 1991; CBI Volume 1, Appendix F). Thirteen metabolites were isolated and identified from urine samples. The metabolite profile indicated that the relative quantities of certain metabolites varied at doses greater than 100 mg/kg chlorpropham. The authors concluded that the maximum tolerated dose (MTD) was >100 mg/kg.

2. Elimination and Recovery

There were no major dose- or sex-related differences in the elimination of chlorpropham following oral or intravenous dosing. The major route of excretion was the urine. After 7 days, the mean total recoveries of radioactivity ranged from 96.29% to 101.83% of the administered dose; 90.29-96.56% of the dose was excreted in the urine (Table 1). Most of the radioactivity (82.28-92.34%) in the urine for all oral dosing groups was recovered within 24 hours postexposure. The feces was a minor excretion route of chlorpropham. After 7 days postexposure, 4.89-7.27% of the administered dose was detected in the feces for the oral dosing groups. The time pattern of chlorpropham excretion in the urine revealed peak elimination at 4-12 hours postexposure for the two low-dose groups (48.90-61.96% of the administered dose) and 8-24 hours for the high-dose group (59.27-64.14%) (Table 2).

The amount of chlorpropham recovered in the urine after intravenous dosing was similar to the amount recovered after oral dosing. Following intravenous dosing of 0.5 mg/kg chlorpropham, mean 7-day recoveries were high; 93.27% and 95.04% of the administered dose for males and females, respectively, with most of the recovery occurring within 24 hours. After 7 days postexposure, recovery in the urine and feces was 88.79% and 4.32% of the administered dose, respectively, for the male rats and 90.67% and 4.23%, respectively, for the female rats.

3. Tissue Distribution

For the oral and intravenous dosing groups, the mean radioactivities recovered in the tissues were negligible. At 7 days postexposure, almost all tissues contained nondetectable levels of radioactivity. The detection limit was not specified. The total 7-day recovery in the tissues, including the carcass, was 0.13-0.42% of the administered dose. The tissues with the highest radioactivity levels contained 0.01-0.02% of the administered dose and the carcass contained 0.12-0.41%. The ^{14}C-residues did not exceed 0.05 ppm for the oral low-dose groups or the intravenous group and did not exceed 0.9 ppm for the oral high-dose group.

4. Metabolism

Of the 22 products detected by HPLC, 13 radioactive bands (accounting for >95% of radioactivity) and the parent compound were identified by TLC in the urine and feces of rats (Table 3 and 4). At 24 hours postexposure, unmetabolized chlorpropham represented a negligible amount of the radioactivity in the feces (0.11-1.77% of the administered dose) and was not detected in the urine.

Following oral exposure, the major metabolites identified in the urine included 4'-hydroxychlorpropham (CIPC-31) (6.14-16% of dose), 3'-chloro-4'-hydroxyacetanilide-O-sulfonic acid (A-4-4-B) (8.89-19.25%), and 4'-hydroxychlorpropham-O-sulfonic acid (A-3-E) (32.95%-46.29%) (Tables 2 and 3). 3-Chloroaniline (CIPC-26) represented 0-3% in low-dose groups. The three glucuronide conjugates (each representing less than 6% of the administered dose) included 4'hydroxychlorpropham-O-glucuronic acid (A-6-2-A), 3'-chloro-4'-hydroxyacetanilide-O-glucuronic acid (A-7-1-A), and 3-chloro-4-hydroxyaniline-N-glucuronic acid-4-O-sulfonic acid (A-3-A-1). In the feces, the metabolites represented a small amount of the administered dose since total radioactivity recovered in the feces was less than 8% of the dose. The major metabolites were 4'-hydroxychlorpropham (CIPC-31) (1.25-2.67% of the administered dose), 3'-chloro-4'-hydroxyacetanilide (CIPC-25) (0.02-0.24%), and 1,4'-dihydroxychlorpropham (A-2-3-B) (0.1-0.35%).

The metabolic pattern of chlorpropham in rats following intravenous dosing was similar to the pattern observed after oral dosing. At 24 hours following the intravenous dosing of 0.5 mg/kg to rats, a mean radioactivity of 39.88-43.90% of administered dose was recovered as metabolite A-3-E in the urine (Table 2). Metabolites A-4-4-B, CIPC-31, and A-4-3-C represented 18.51-19.25%, 8.46-10.25%, and 5.07-5.15% of the administered dose, respectively, in the urine. The other metabolites were less than 5% of the dose. The feces contain approximately 1.85% of CIPC-31. CIPC-25 and A-2-3-B (each <0.3% of the dose) were the only other metabolites detected in feces. The parent compound was not detected in the urine or feces of the animals dosed intravenously.

D. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES

The authors concluded that chlorpropham is eliminated almost entirely in the urine of rats. Most of the radioactivity was recovered within 24 hours after exposure which indicates rapid and extensive absorption of this chemical following oral administration. In the feces, a low amount of radioactivity was recovered (less than 8% of administered dose). There were no major sex- or dose-related differences in the absorption, distribution, metabolism, and excretion of chlorpropham. Seven days following single and repeated oral dosing of chlorpropham, most tissues showed negligible activities (0% of administered dose). No major sex- or dose-related differences in the tissue distribution pattern were evident. The pattern of the metabolite radioactivity in the urine and feces was relatively similar among oral and intravenous groups. The authors reported that chlorpropham expired as CO_2 is not expected to be the route of elimination as indicated from the preliminary study (Wu 1991).

The majority of the recovered metabolites were conjugates of sulfate (58-68% of the dose) and glucuronide (0-7% of the dose). The results are consistent with earlier findings (Fang et al. 1974) indicating that chlorpropham is metabolized in the rat by hydrolysis, oxidation, and acetylation. The authors proposed three major metabolite pathways for chlorpropham: hydroxylation at 4'-position to conjugation; oxidation of isopropyl side chain to form isopropanol and isopropionate moieties; and decarbanilation to form 3-chloroaniline then N-acetylation, 4'-hydroxylation, and conjugation (Figure 1).

Quality assurance statements for the study were signed on August 20, 1991 (Volume 1) and May 2, 1991 (Volume 2). The statements of Good Laboratory Practices compliance for the study were signed on August 26, 1991.

E. CONCLUSIONS BASED ON REVIEWERS' DISCUSSION AND INTERPRETATION OF DATA

The study adequately described the absorption, distribution, metabolism, and excretion of [^{14}C]chlorpropham in rats following single and repeated oral exposure, as well as single intravenous injection. The data indicate that labeled chlorpropham is rapidly and completely absorbed from the gastrointestinal tract and that the urine is the primary route of excretion. The oral absorption rate could not be determined because the peak blood levels were not measured in the study. Biliary excretion is unlikely to occur since fecal elimination was minimal and the intravenous dosing resulted in >90% recovery in the urine. The low tissue levels of radioactivity, as well as the rapid elimination, demonstrate that bioaccumulation and retention of chlorpropham and/or its metabolites are low in rats. The recovery of the administered radioactivity is acceptable (90.29-99.79%) for all dose groups. The metabolism of chlorpropham was extensive following oral and intravenous dosing as indicated by a minimal recovery of 0-2% of the unmetabolized parent compound in the feces and an undetected amount (0%) in the urine

for the dosing groups at 7 days postexposure. There were 22 radioactive components detected by TLC, but only 13 were identified as metabolites of chlorpropham. The proposed metabolic pathway appears to be adequately described from the study results. No major sex-, dose-, and route-related differences in the absorption, distribution, and metabolism of chlorpropham in rats were found in this study, although there was a slight route- and sex-related difference in excretion.

REFERENCES

Fang, S.C., E. Fallin, M.L. Montgomery, and V.H. Freed. 1974. Metabolic studies of 14C-labeled propham and chlorpropham in the female rat. Pest Biochm Physiol 4: 1-11.

Liu, D.W. 1991. Metabolism of 14C-Chlorpropham in Rats: Preliminary Metabolite Isolation and Identification Study. Study No. XBL90050. Report No. RPT0057. June 10, 1991.

Wu, D. Metabolism of 14C-Chlorpropham in Rats: Preliminary Range-Finding Study. Study No. XBL89071. Report No. RPT0032. XenoBiotic Laboratories, Inc., Princeton, NJ. June 10, 1991.

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TABLE 1. Mean Percent Recovery of Radioactivity 7 Days After Oral or Intravenous Administration of Chlorpropham to Rats

Dose Group	Sex	Percentage of Administered Dose Recovered			
		Urine	Feces	Tissues (and carcass)	Total[a] Recovery
5 mg/kg (single oral)	Male[b]	93.12	7.19	0.20	100.51
	Female	90.53	5.38	0.37	96.29
200 mg/kg (single oral)	Male	95.81	6.55	0.13	102.49
	Female	90.29	7.27	0.42	97.98
5 mg/kg[c] (repeated oral)	Male	96.56	5.13	0.14	101.83
	Female	93.59	4.89	0.32	98.80
0.5 mg/kg (intravenous)	Male	88.79	4.32	0.17	93.27
	Female	90.67	4.23	0.13	95.04

[a]Based on individual means

[b]5 animals/sex

[c]Animals were given 5 mg/kg/day unlabeled chlorpropham for 14 days and a single dose of 5 mg/kg [^{14}C]chlorpropham on day 15.

Source: CBI Volume 2; Tables 41-48, pp. 400-407

TABLE 2. Excretion Times of Chlorpropham in the Urine of Rats After Oral Administration

	(values given as % of administered dose)											
	5 mg/kg (single)			200 mg/kg (single)			5 mg/kg (repeated)					
Collection Time	Male		Female	Male		Female	Male		Female			
0-4	7.81	92.2	20.47	79.5 5.90		94.1 12.19	87.8 18.34		81.7 17.50		82.5	
4-8	39.56	47.4 52.6	22.41	42.4 57.1	20.93	26.8 73.2	10.82	23.0 77.0	40.71	50.9	49.1	38.50 56.0 44.0
8-12	22.40	69.8 30.2	26.49	69.4 30.6	33.72	60.5 39.5	26.10	49.1 50.9	18.91	77.9	22.1	17.54 73.5 26.5
12-24	19.29	89.1 10.9	14.39	83.8 16.2	30.42	90.9 9.1	33.17	82.3 17.7	14.38	92.3	7.7	13.63 87.1 12.9
24-36	2.15	91.3 8.7	3.14	86.9 13.1	2.68	93.6 6.4	3.64	85.9 14.1	2.03	94.3	5.7	3.21 90.3 9.7
36-48	0.73		0.93	0.69		1.73	0.73		1.37			
48-72	0.46		1.01	0.55		1.15	0.53		0.87			
72-96	0.29		0.71	0.27		0.44	0.24		0.35			
96-120	0.19		0.37	0.32		0.36	0.30		0.23			
120-144	0.11		0.26	0.13		0.22	0.22		0.24			
144-168	0.12		0.32	0.14		0.30	0.11		0.13			
Final	0.01		0.01	0.05		0.17	0.05		0.03			

Source: CBI Tables 2, 5, 8, 11, 14, 17; CBI pp. 361, 364, 367, 370, 373, 376

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TABLE 3. Distribution of Metabolites in Urine and Feces 24 Hours After Oral Administration of Chlorpropham[a]

	5 mg/kg (single oral)				5 mg/kg (repeated oral)				200 mg/kg (single oral)				0.5 mg/kg (intravenous)			
	Male		Female		Male		Female		Male		Female		Male		Female	
Metabolites	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces
A-2-3-B	1.32	0.35	1.02	0.23	1.46	0.25	2.78	0.15	1.64	0.23	0.49	0.10	2.00	0.17	1.29	0.22
A-3-A-1	--	--	4.31	--	--	--	--	--	3.86	--	--	--	--	--	0.68	--
A-3-E	32.95	--	40.00	--	39.09	--	34.08	--	35.71	--	46.29	--	39.88	--	43.90	--
A-4-3-C	5.98	--	6.88	--	6.80	--	8.06	--	8.11	--	3.13	--	5.07	--	5.15	--
A-4-4-B	18.76	0.11	15.14	0.04	16.00	--	13.75	0.04	13.30	0.03	8.89	0.02	19.25	--	18.51	--
A-5-C-1-A	3.38	--	4.74	--	4.12	--	6.13	--	1.73	--	3.17	--	4.13	--	4.56	--
A-6-2-A	5.60	0.33	--	0.08	4.25	--	0.57	--	2.05	0.47	--	0.07	0.20	--	0.00	0.02
A-7-1-A	2.00	0.03	0.39	--	1.73	--	--	--	0.94	--	--	--	0.39	--	0.00	--
CIPC-22	0.53	0.07	--	--	--	--	1.53	--	0.65	0.11	--	--	0.58	--	0.00	--
CIPC-25	0.40	0.24	0.76	0.12	0.92	0.10	0.78	0.09	0.43	0.13	0.69	0.05	1.32	0.09	1.59	0.02
CIPC-26	2.29	--	1.22	--	0.92	--	--	--	--	--	--	--	--	--	0.14	--
CIPC-30	1.44	--	1.38	--	1.24	--	2.48	--	6.22	--	4.59	--	0.37	--	1.64	--
CIPC-31	12.68	2.60	6.14	1.25	14.85	2.40	16.00	2.08	15.74	2.67	14.09	1.41	10.25	1.84	8.46	1.87
Unknown-1	--	--	0.54	--	0.65	--	--	--	0.59	--	0.38	--	0.31	--	0.22	--
Unknown-2	--	--	0.59	--	--	--	--	--	--	--	--	--	--	--	0.00	--
Unknown-4	0.61	--	--	--	0.33	--	--	--	--	--	--	--	0.81	--	0.00	--
Unknown-5	--	--	--	--	--	--	1.00	--	--	--	--	--	0.33	--	0.76	--
Unknown-6	0.71	--	0.66	--	--	--	--	0.03	--	--	--	--	--	--	0.00	--
Unknown-7	0.41	--	--	--	--	--	--	--	--	--	--	--	--	--	0.00	--
Unknown-8	--	--	--	--	--	--	--	--	--	--	0.57	--	--	--	0.00	--
Parent Compound	--	--	--	0.36	--	0.21	--	--	--	0.11	--	1.77	--	--	--	--
Total	89.05	3.72	83.77	2.08	92.35	2.97	87.17	2.40	90.96	3.76	82.29	3.42	84.89	2.10	86.90	2.13

[a]Values given as percentage of administered dose

Source: CBI Volume 1, Tables IX, XII, pp. 39 and 42

TABLE 4. Thirteen Metabolites of Chlorpropham Identified in Urine and Feces

Metabolite Code	Chemical Name
A-2-3-B	1,4'-Dihydroxychlorpropham
*A-3-A-1	3-Chloro-4-hydroxyaniline-N-glucuronic acid-4-O-sulfonic acid
*A-3-E	4'-Hydroxychlorpropham-O-sulfonic acid
*A-4-3-C	1,4'-Dihydroxychlorpropham-4'-O-sulfonic acid
A-4-4-B	3'-Chloro-4'-hydroxyacetanilide-O-sulfonic acid (A-5-B-1)
*A-5-C-1-A	Chlorpropham carboxylic acid
A-6-2-A	4'-Hydroxychlorpropham-O-glucuronic acid (A-7-2-A)
A-7-1-A	3'-Chloro-4'-hydroxyacetanilide-O-glucuronic acid
CIPC-22	1-Hydroxychlorpropham
CIPC-25	3'-Chloro-4'-hydroxyacetanilide (A-2-2-A)
*CIPC-26	3-Chloroaniline
*CIPC-30	3-Chloro-4-hydroxyaniline-O-sulfonic acid, Potassium salt
CIPC-31	4'-Hydroxychlorpropham (A-1-1-B)

* Detected in the urine only

Source: Table II, pp. 29-32

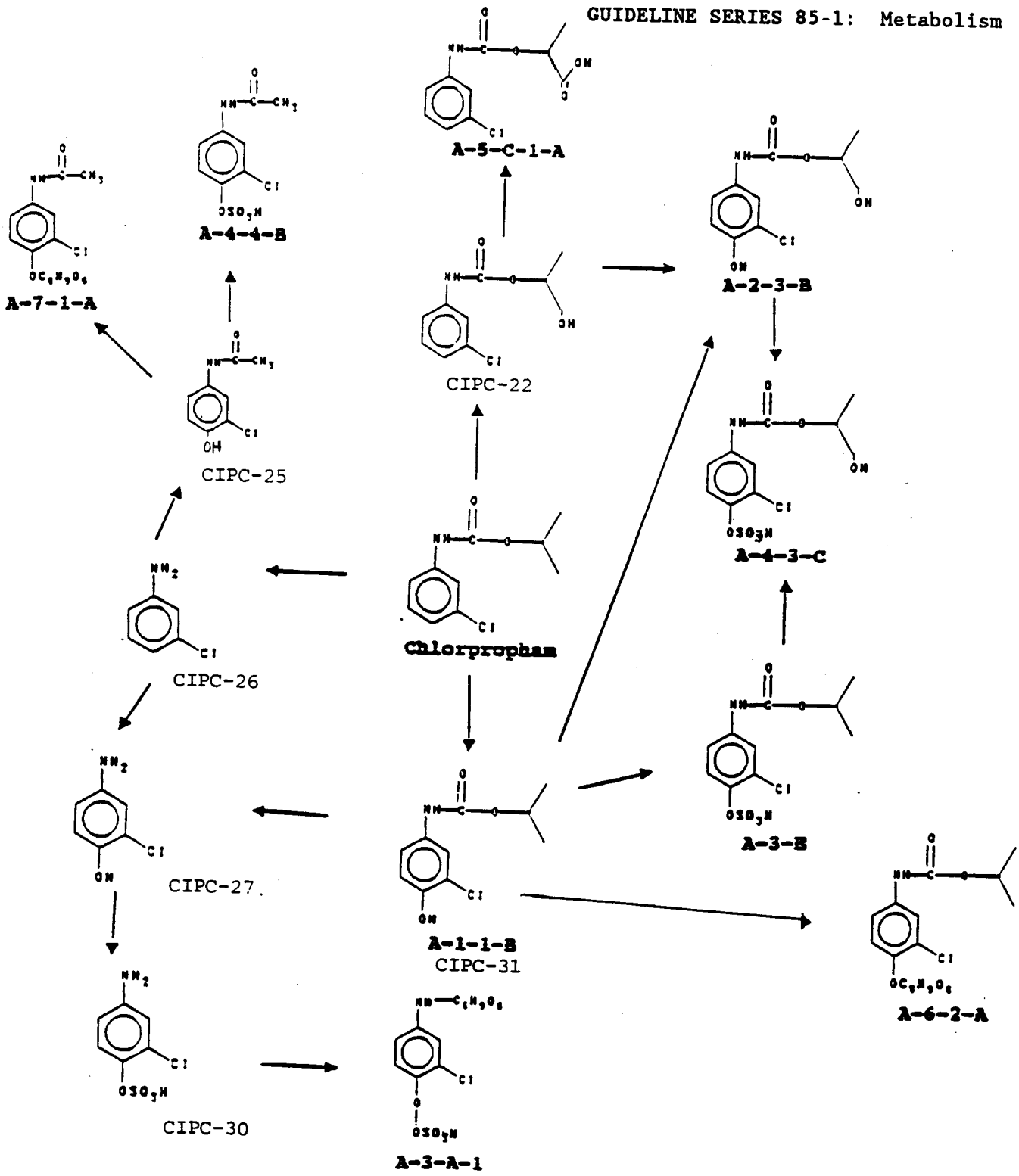

FIGURE 1. Proposed Metabolic Pathway of Chlorpropham in Rats (refer to Table 3 for the chemical names of the metabolites)

Source: CBI Volume 1, Figure 12, p. 55