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

JUN 15 1993

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: EPA ID# 018301, Chlorpropham: CIC Review of the subchronic toxicity study in mice with Chlorpropham (MRID# 418993-01).

Shaughnessy #: 018301.
Caswell#: 510A.
HED Project#: 1-1510.
DP Barcode: D165224.
Case#: 818637.
Submission#: S397515.

From: David G Anderson, PhD 4/26/93
Section 3, Toxicology Branch-1
HED (H7509C)

To: Walter Waldrop/Venus Eagle, PM-71,
Reregistration Branch
SRRD (H7508C)

Thru: Karen Hamernik, PhD 4/26/93
Acting Section 3 Head
Toxicology Branch-1,
HED (H7509C)

Data Reviewed:
MRID# 418993-01. R.W. Krohomer. September 28, 1990. 90-Day Toxicity Evaluation of Chlorpropham in the Mouse. Conducted at T.P.S., Inc. for Chlorpropham Task Force, John Wise & Associates, Ltd. Lab ID 393H-001-034-89.

CONCLUSIONS: Chlorpropham was administered via the diet to 10 CD-1™ mice per sex per group for 90-days at dose levels of 0, 105, 210, 420 and 840 mg/kg/day. The nominal average daily intake values were 0, 105, 214, 436 and 856 mg/kg/day in males and 0, 111, 217, 443 and 857 mg/kg/day in females. Chlorpropham exhibited hematological toxicity with a NOEL of 420 mg/kg/day and a LOEL of 840 mg/kg/day. The probable cause of the toxicity, increased methemoglobin levels, was not directly measured.

NOEL: 420 mg/kg/day - Equivalent to 436 mg/kg/day in males and 443 mg/kg/day in females. No treatment related effects were observed.

LOEL: 840 mg/kg/day - Equivalent to 856 mg/kg/day in males and 857 mg/kg/day in females. All males and all but 1 female showed an increased incidence of darker-than-normal blood. Also at 840 mg/kg/day dark eyes and pale extremities were noted in all males. Darker-than-normal blood and statistically significantly increased MCH and MCHC in both males and females. Statistically significantly increased reticulocyte count, absolute spleen weights, relative weights and spleen/brain weight ratios occurred in males. Increased extramedullary hematopoiesis in the livers and spleens, hemosiderosis in the spleens, and increased cellularity and erythropoiesis in the bone marrow of males and females.

Core Classification: Supplementary. The study is not acceptable under guideline 82-1 for a 90-day study in rodents. No clinical chemistry determinations were conducted. In addition, hematology should have included analysis of methemoglobin levels. However, a 90-day study in mice may be unnecessary, if an acceptable NOEL can be established from the chronic feeding study in rats when submitted.

CMemo on a CIC-DER for a 90-day toxicity study in mice/MRID# 418993-01/B:\CHLORV25.10A\CM90DMO1.192/DANDERSON/11/21/92(Edited 4/26/93).*

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DOC930157

FINAL

DATA EVALUATION REPORT

Chlorpropham

Study Type: Subchronic Oral Toxicity in Mice

Prepared for:

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

Prepared by:

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9300 Lee Highway
Fairfax, VA 22031-1207

October 26, 1992

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Carrie Rabe, Ph.D.

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Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-43
Clement Number: 93-53
Project Officer: James Scott

Guideline Series 82-1 -- Subchronic Oral Toxicity
in the Rodent: 90-Day Study

EPA Reviewer: David Anderson, Ph.D.
Tox. Branch I, Review Section III
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Signature: David R Anderson
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Date: 4/26/93

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Oral Toxicity in Mice

TEST MATERIAL: Chlorpropham

Tox. Chem. Number: 510A

SYNONYMS: CIPC

Shaughnessy Number: 018301

CAS Number: 101-21-3

STUDY NUMBER: 393H-001-034-89

MRID Number: 418993-01

SPONSOR: Chlorpropham Task Force
John M. Wise Associates
P.O. Box 301
Liberty, Missouri 64068

TESTING FACILITY: Toxicology Pathology Services, Inc.
10424 Middle Mt. Vernon Road
P.O. Box 333
Mt. Vernon, Indiana 47620

TITLE OF REPORT: 90 Day Subchronic Toxicity Evaluation of Chlorpropham in the Mouse

AUTHOR: R.W. Krohmer

REPORT ISSUED: Study completed September 28, 1990

CONCLUSIONS: Chlorpropham was administered via the diet to CD-1® mice for 90 days at dose levels of 0, 105, 210, 420, and 840 mg/kg/day. The nominal average daily intake values were 0, 105, 214, 436, and 856 mg/kg/day in males, and 0, 111, 217, 443, and 857 mg/kg/day in females. Chlorpropham exhibited hematological toxicity with a NOEL of 420 mg/kg/day and a LOEL of ~~840~~ mg/kg/day. The probable cause of the toxicity, increased methemoglobin levels, was not directly examined. DRA 4/26/93

105 mg/kg/day -- Equivalent to 105 mg/kg/day in males and 111 mg/kg/day in females. No treatment-related effects were observed.

210 mg/kg/day -- Equivalent to 214 mg/kg/day in males and 217 mg/kg/day in females. No treatment-related effects were observed.

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420 mg/kg/day -- Equivalent to 436 mg/kg/day in males and 443 mg/kg/day in females. An increased incidence of darker-than-normal blood in both males and females.

840 mg/kg/day -- Equivalent to 856 mg/kg/day in males and 857 mg/kg/day in females. Dark eyes and pale extremities in all males. Darker-than-normal blood and significantly increased MCH and MCHC in males and females. Significantly increased reticulocyte count in males. Significantly increased absolute spleen weights, spleen-to-body-weight ratios, and spleen-to-brain-weight ratios in males. Increased extramedullary hematopoiesis in the livers and spleens, hemosiderosis in the spleens, and increased cellularity and erythropoiesis in the bone marrow of males and females.

Based on the hematological findings in male and female mice, the LOEL for this study was 840 mg/kg/day. The NOEL for this study was 420 mg/kg/day. However, the possibility of a lower NOEL and LOEL cannot be eliminated because a more sensitive endpoint would have been blood methemoglobin levels, and these were not measured in this study. DRA 4/26/93

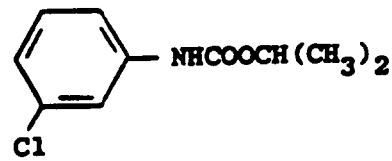
CORE CLASSIFICATION: the additional information indicated: Supplementary. No clinical chemistry determinations were conducted. ~~Stability studies must be submitted with the study.~~ In addition, hematology should have included analysis of methemoglobin levels. However, a 90-day study in mice may be unnecessary, if an acceptable NOEL can be established from the chronic feeding study in rats when submitted and evaluated. DRA 4/26/93

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Chlorpropham (technical grade)

Formula: $C_{10}H_{12}ClNO_2$; (3-chlorophenyl)carbamic acid 1-methylethyl ester



Lot number: 14065 L 89

Purity: 96.2% (weeks 1-3), 97.1% (weeks 4-13)

Physical property: White crystalline solid

Stability: Data on stability were reported to be the responsibility of the sponsor.

2. Rationale for Dose Selection

Dietary levels for the current study were reported to have been selected by the sponsor based on the results of previous studies. No information on these previous studies was provided.

3. Test Article Analyses for Purity and Stability

Test diets containing chlorpropham were prepared weekly by first dissolving the test material in corn oil and then mixing this solution with the basal diet in a Hobart mixer for approximately 15 minutes. This preblend was then mixed with the appropriate amount of basal diet to achieve the desired test material concentrations. The diets of the control animals contained an amount of corn oil equivalent to that in the highest dietary level. The diets were stored in closed containers at room temperature.

No information was provided regarding stability of the undiluted test material over the duration of the study. In addition, no information was provided regarding stability of the test material in prepared diets.

Homogeneity and actual concentrations of chlorpropham in the diet for all dietary levels were determined at weeks 1, 2, 3, 4, 8, and 12 using HPLC analysis following methanol, methylene chloride, and hexane extraction of the samples. The amounts of chlorpropham present in the diet samples were determined using a calibration curve and blank diet reference standard. Diets were homogenous and actual concentrations ranged between 96% and 107% of the intended levels.

4. Animals

CD-1® mice were purchased from Charles River Laboratories (Portage, MI) and acclimated for 14 days prior to the start of the study. A total of 150 mice (75 males and 75 females) were assigned randomly by computer to five study groups (15/sex/group). No statistically significant differences in body weight between the groups existed on the day prior to the start of the study. At the initiation of the study, the animals were approximately 6 weeks of age, and weight ranges were 25.6-32.2 g for males and 19.0-25.6 g for females. Animals were housed individually in stainless steel cages with wire mesh bottoms, and food (Purina® Certified Rodent Chow #5002) and tap water were provided ad libitum throughout the study. The animal room was operated on a 12-hour light/dark cycle, and temperature and relative humidity were maintained at 60°-80°C and 35%-75%, respectively. Mice were uniquely identified through the use of cage tags and tail tattoos.

5. Statistical Methods

Body weight, food consumption, organ weight, and hematology data were analyzed using Dunnett's Multiple Comparison test.

6. General Observations

(a) Mortality/moribundity/survival

Animals were observed twice per day for mortality and moribundity.

No treatment-related effects on mortality were observed. One female at the lowest dose tested was found dead during study week 9 and one female at the highest dose tested was found dead during study week 13. The cause of death was not apparent after gross or histopathological examination.

(b) Clinical signs

Animals were observed twice per day for overt signs of toxicity. Detailed observations for signs of toxicity were performed weekly.

All of the males at the highest dose tested had dark eyes and pale extremities. The dark eyes were first noted at week 7, and the pale extremities were first noted between weeks 5 and 7. These signs continued until the end of the study. No mice from any other group showed these signs.

(c) Body weights/food consumption/feed efficiency/test article intake

Body weights--Body weights were measured prior to randomization into study groups and once weekly after the start of the study. Both summary and individual body weight and body weight gain data were provided in the study report.

No treatment-related effects on mean body weight or body weight gain were observed.

Food consumption--Measurements of food consumption were made once weekly. Both summary and individual data were provided in the study report.

No statistically significant effects on food consumption were observed.

Feed efficiency--No data on feed efficiency were provided in the report.

Test article intake--The intended doses of chlorpropham for this study were 0, 105, 210, 420, and 840 mg/kg/day. The concentration of test material in the diet was adjusted weekly using food consumption data from the previous week to more closely approximate the intended test material intakes. The actual doses consumed were calculated weekly by the author based on the nominal dietary concentrations and food consumption and body weight data.

Mean test article intakes were 0, 105±5, 214±15, 436±50, and 856±77 mg/kg/day for males, respectively, and 0, 111±11, 217±17, 443±45, and 857±88 for females, respectively.

(d) Ophthalmoscopic examination

Ophthalmic examinations were conducted on all animals pretest and on all surviving animals during week 13. No treatment-related effects were observed.

7. Clinical Pathology

Hematological analyses were performed on all surviving animals at study termination. Animals were fasted overnight prior to blood collection. Subdivision F (November 1984) Guidelines also recommend clinical chemistry values from all animals of each sex in each group. However, no clinical chemistry analyses were performed in this study. The parameters marked with an X below were examined.

Hematology

X Hematocrit (HCT)*	X Leukocyte differential count*
X Hemoglobin (HGB)*	X Mean corpuscular HGB (MCH)
X Leukocyte count (WBC)*	X Mean corpuscular HGB concentration (MCHC)
X Erythrocyte count (RBC)*	X Mean corpuscular volume (MCV)
X Platelet count*	
X Reticulocyte count	

* Recommended by Subdivision F (November 1984) Guidelines

Statistically significant increases in MCH (5%-6% increase) and MCHC (3%-5% increase) were observed in high-dose males and females when compared to controls. In addition, a statistically significant increase in reticulocyte count (45% increase) was observed in high-dose males. Darker-than-normal blood color was also noted in male and female mice at doses as low as 420 mg/kg/day. Summary data for MCH, MCHC, reticulocyte count, and blood color are presented in Table 1.

8. Sacrifice and Pathology

Complete gross examinations were performed on all animals at terminal sacrifice, as well as on the two animals that died on study. All tissues were preserved in 10% phosphate-buffered formalin. All tissues from high-dose and control animals marked with an X below were examined histologically. In addition, the liver, spleen, sternum (with bone marrow), and tissues with gross lesions were examined for all animals. Organs indicated by XX below were weighed for all animals.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	Aorta*	XX Brain
X Salivary glands*	XX Heart*	X Peripheral nerve (sciatic)*
X Esophagus*	X Bone marrow*	X Spinal cord (three levels)
X Stomach*	X Lymph nodes*	XX Pituitary*
X Duodenum*	XX Spleen	X Eyes*
X Jejunum*	X Thymus	
X Ileum*		
X Cecum*	Urogenital	
X Colon*		Glandular
X Rectum	XX Kidneys*	
XX Liver*	X Urinary bladder*	XX Adrenals*
X Gallbladder*	XX Testes (with epididymides)*	X Harderian gland
X Pancreas*	X Prostate	XX Thyroids (with parathyroids)*
	X Seminal vesicle	X Mammary glands
Respiratory	XX Ovaries	
	X Uterus	
X Trachea*		
X Lung*		

Other

X Bone (sternum) and marrow*
X Skeletal muscle*
X Skin
X All gross lesions and masses*

* Recommended by Subdivision F (November 1984) Guidelines

(a) Macroscopic

The incidence of gross lesions was low overall, and none of the effects appeared to be treatment related. One of two mice that escaped from their cages and were recaptured was found to be pregnant at necropsy.

(b) Organ weights and body weight ratios

Significant increases in the absolute spleen weights, spleen-to-body-weight ratio, and spleen-to-brain-weight ratios were observed in males at 840 mg/kg/day. Significant increases in the absolute spleen weights and spleen-to-brain-weight ratios were also observed in males at 210 mg/kg/day. However, the absolute and relative spleen weights at 420 mg/kg/day were not significantly elevated. Spleen weights in mice can be quite variable; therefore, the apparent increases observed at 210 mg/kg/day may have been spurious.

Other statistically significant organ weights are considered to be incidental. Summary absolute and relative organ weight data are presented in Table 2.

(c) Microscopic

Histopathologic data were not analyzed statistically. However, increases (1) in the incidence of extramedullary hematopoiesis in the liver, (2) the severity of extramedullary hematopoiesis in the spleen, (3) the incidence of hemosiderosis in the spleen, (4) the severity of cellularity of the bone marrow, and (5) the incidence of increased erythropoiesis in the bone marrow were observed in both male and female mice at the highest dose tested. Summary histopathologic data are presented in Table 3.

- -

A signed Good Laboratory Practice Compliance Statement, a signed Quality Assurance Statement, and a list of Quality Assurance inspections were included in the report.

B. DISCUSSION

Review of the final report and supporting data indicate that the reporting of the results was accurate. However, this study deviated from Subdivision F (November 1984) Guidelines in that no clinical chemistry determinations were performed. In addition, no stability data for the test material in the diets were provided. Thus, it is unclear whether test diets contained comparable amounts of test material at the beginning and end of each feeding period. Also, at least two mice escaped for a long enough period of time for one of the mice to become pregnant. ~~Insufficient data were provided regarding the escape to determine how long the animals were free or whether it was an isolated incident. If other escapes occurred, it could indicate poor animal management techniques.~~ Therefore, the information in this study was classified as Core Supplementary.

4/26/93

The results of this study indicate a toxic effect of chlorpropham on the blood. At the highest dose tested, males and females had darker-than-normal blood, increased extramedullary hematopoiesis in the liver and spleen, increased hemosiderosis in the spleen, increased cellularity and erythropoiesis in the bone marrow, and significantly increased MCH and MCHC. In addition, males exhibited dark eyes, pale extremities, significantly increased reticulocyte count, and significantly increased absolute and relative spleen weights. All of these signs are consistent with methemoglobinemia, the resulting hemolysis, and compensatory increased red blood cell production. The hypothesis that the effects observed are associated with methemoglobinemia are supported by the likelihood that the metabolite of chlorpropham, 4-hydroxy-3-chloroaniline, may oxidize hemoglobin to methemoglobin (Gosselin et al., 1984; see attached).

Methemoglobin levels were not assayed in this study. This would have been the most direct and sensitive assay to determine whether chlorpropham was resulting in methemoglobinemia in the mice in this study. If changes in methemoglobin levels had been observed, that would have been the ideal endpoint for use in determining a NOEL and LOEL for chlorpropham. Because

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methemoglobin levels were not measured in this study, other less sensitive endpoints were used to set the NOEL and LOEL.

Some uncertainty exists regarding the NOEL and LOEL for this study. At 420 mg/kg/day, both male and female mice exhibited darker-than-normal blood. However, this is a subjective finding and is not supported by other hematological findings. Therefore, the reviewers conclude that the LOAEL for hematological effects 840 mg/kg/day.

Study Classification: Core Supplementary

LOEL: 840 mg/kg/day (hematological effects)

NOEL: 420 mg/kg/day

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TABLE 1. Selected Hematology Parameters from Mice Given Diets Containing Chlorpropham for 90 Days[a,b]

Parameter	Dose (mg/kg/day)				
	0	105	210	420	840
			Males		
Darker-than-normal blood[c] (incidence)	0/15	0/15	1/14	10/15	15/15
MCH (pg)	15.4±0.7	15.6±0.7	15.4±0.8	15.8±0.6	16.1±0.7*
MCHC (g/dL)	33.2±0.5	33.7±0.7	33.3±0.6	33.7±0.6	34.7±1.1**
Reticulocytes (%)	2.0±0.4	1.9±0.4	2.0±0.5	2.2±0.9	2.9±0.8**
			Females		
Darker-than-normal blood[c] (incidence)	0/15	0/14	0/15	5/13	12/13
MCH (pg)	15.7±0.6	16.1±1.2	16.0±0.6	15.8±0.9	16.7±0.8**
MCHC (g/dL)	34.0±0.7	33.7±0.6	34.0±0.6	34.1±0.8	35.1±0.7**
Reticulocytes (%)	2.1±0.6	3.1±4.3	2.0±0.6	2.6±2.0	2.7±0.6

aData extracted from Study #393H-001-034-89, Table 5 and Appendix VI.
[b]Mean±SD; N=15 except N=14 for males at 210 mg/kg/day and females at 105 mg/kg/day and N=13 for females at 420 mg/kg/day and 840 mg/kg/day.
[c]Not analyzed statistically

* Significantly different from control; p≤0.05
** Significantly different from control; p≤0.01

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TABLE 2. Selected Absolute and Relative Organ Weights of Mice Given Diets Containing Chlorpropham for 90 Days[a,b]

Parameter	Dose (mg/kg/day) 0	105	210	420	840
			Males		
Spleen					
Absolute Weight (g)	0.068±0.021	0.075±0.021	0.089±0.023*	0.083±0.011	0.100±0.027**
Spleen-to-Body-Wt. (%)	0.200±0.060	0.214±0.067	0.255±0.057	0.235±0.036	0.291±0.085**
Spleen-to-Brain-Wt. (%)	13.09±3.56	14.70±4.39	17.55±4.53*	17.21±3.70	19.51±7.07**
			Females		
Spleen					
Absolute Weight (g)	0.080±0.019	0.092±0.046	0.074±0.014	0.091±0.039	0.100±0.028
Spleen-to-Body-Wt. (%)	0.290±0.053	0.348±0.180	0.268±0.050	0.334±0.110	0.353±0.099
Spleen-to-Brain-Wt. (%)	14.92±3.60	18.09±10.73	14.34±2.53	17.90±7.79	19.25±4.88

aData extracted from Study #393H-001-034-89, Table 8 and Appendix VII.
[b]Mean±SD; N=15 except N=14 for 105- and 840-mg/kg/day females

* Significantly different from control; p≤0.05
** Significantly different from control; p≤0.01

TABLE 3. Selected Histopathological Findings from Mice Given Diets Containing Chlorpropham for 90 Days[a]

Parameter	Dose (mg/kg/day) 0	105	210	420	840
			Males		
Liver					
Extramedulary Hematopoiesis					
Minimal	2/15	1/15	1/15	1/15	4/15
Spleen					
Extramedulary Hematopoiesis					
Minimal	13/15	14/15	13/15	14/15	0/15
Slight	2/15	1/15	2/15	1/15	14/15
Moderate	0/15	0/15	0/15	0/15	1/15
Hemosiderosis					
Minimal	0/15	0/15	0/15	2/15	6/15
Bone Marrow					
Cellularity					
Moderate	13/15	14/15	13/15	14/15	0/15
Marked	2/15	1/15	2/15	1/15	15/15
Increased Erythropoiesis	0/15	0/15	0/15	0/15	15/15

TABLE 3 (continued)

Parameter	Dose (mg/kg/day) 0	105	210	420	840
			Females		
Liver					
Extramedulary Hematopoiesis					
Minimal	0/15	1/15	1/15	2/15	9/15
Spleen					
Extramedulary Hematopoiesis					
Minimal	14/15	14/15	15/15	14/15	0/15
Slight	1/15	1/15	0/15	1/15	15/15
Moderate	0/15	0/15	0/15	0/15	0/15
Hemosiderosis					
Minimal	1/15	4/15	2/15	1/15	9/15
Bone Marrow					
Cellularity					
Moderate	15/15	13/14	14/14	13/14	0/15
Marked	0/15	1/14	0/14	1/14	15/15
Increased Erythropoiesis	0/15	1/14	0/14	1/14	15/15

[a]Data extracted from Study #393H-001-034-89, Appendix IX

Clinical Toxicology of Commercial Products

1984 *Fifth Edition*

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1225 1225 2,4,5-Trichlorophenoxy Ethyl Sulfate Sodium Salt

2,4,5-TES, Natrin

Toxicity Rating: 4. Studies in laboratory animals place this weed-killer near the borderline between toxicity classes 3 and 4. It causes moderate skin irritation and severe damage to eyes. Percutaneous absorption is marked in rabbits and a potential hazard in man. Convulsions have been observed in acutely poisoned animals. Not presently registered in the U.S.A.

See also: 2,4-D, *Reference Congener in Section III.*
Ref.: Dernehl, 1957.

Carbamate herbicides

1226 1226 Asulam

Methyl sulfanilylcarbamate, Asulox

Toxicity Rating: 2. This and its acetamide derivative (generic name Carbasulam) are systemic herbicides usually supplied as sodium salts. Low acute oral toxicity (rat oral LD_{50} is greater than 5 gm./kg.). No significant percutaneous absorption. Dogs tolerated daily doses of 500 mg./kg. for 13 weeks without adverse effects.

Ref.: Worthing, 1979.

1227 1227 Barban

4-Chloro-2-butynyl *m*-chlorocarbanilate, 4-Chloro-2-butynyl *N*-(3-chlorophenyl) carbamate, Carbyne

Toxicity Rating: 3. Herbicide for control of wild oats in row crops. Acute oral LD_{50} in rats is variously reported as 600 mg./kg. to 1.5 gm./kg. Weak cholinesterase inhibitor. Large doses are said to cause methemoglobinemia, which may be referable to metabolites (see below). Daily administration of 0.1 LD_{50} to guinea pigs and rabbits for 4 to 6 months is said to have caused fatty dystrophy of the liver and kidneys, hemosiderosis of the spleen and vascular hyperemia of liver, brain, kidneys, spleen, and gastric mucosa. Daily doses of 20 to 40 mg./kg. to rabbits caused a significant decrease in liver glycogen content. Systemic toxicity following prolonged dermal exposures is described. May cause allergic skin reactions in sensitive persons. Barban metabolism yields a variety of compounds, including aniline, *m*-chloroaniline, *p*-aminophenol and *p*-hydroxy barban. If methemoglobinemia is demonstrable, treat patient as for aniline poisoning; see Aniline in Section III. Also consult index for *p*-Aminophenol.

Ref.: Aleksandrova and Klisenko, 1971; Grunow et al., 1970; Gzhegotskii and Dotoshitskii, 1971; Nekrasova and Knysh, 1971; Nekrasova and Razoznaeva, 1971; Riden, 1961.

1228 1228 Carbetamide

N-Ethyllactamide carbanilate, Carbetamex

Toxicity Rating: 3. Persistent herbicide, for use in control of grasses and weeds in legume crops. Moderate acute oral toxicity in mammals (LD_{50} in dogs 1 gm./kg.). Dogs tolerated 13,000 ppm in food for 3 months without ill effects.

Ref.: Worthing, 1979.

1229 1229 Chlorpropham

Isopropyl *N*-(3-chlorophenyl)carbamate, Isopropyl *m*-chlorocarbanilate, CIPC, Metoxon

Toxicity Rating: 3. One of several closely related pre-emergence herbicides containing the carbamate grouping. These herbicides are frequently supplied in mixtures with other compounds such as pyrazon, diuron, endothal or fenuron (see entries in this index). A mitotic poison in plants. Used in the production of truck crops. Moderate to low oral toxicity in mammals (rat oral LD_{50} 1.5 to 5 gm./kg. for chlorpropham, 2.5 gm./kg. for chlorbufam and 5 gm./kg. for propham). Chlorpropham (and presumably the others) was more toxic to rats on a low protein diet. Following administration of single toxic doses of chlorpropham to laboratory animals, initial symptoms included listlessness, ataxia, epistaxis, exophthalmos, hemodacryorrhea and hemorhinorrhea. These progressed to dyspnea, prostration, anuria, glycosuria, proteinuria, hyperthermia, and death. Autopsy findings showed gastroenteritis with occasional congestion of brain, lungs and other organs. Stress response was evident in adrenal, thymus and spleen, while degenerative changes were seen in kidney and liver. Chlorpropham inhibited DNA formation in regenerating rat liver following partial hepatectomy. Chlorpropham and propham (and presumably chlorbufam) are metabolized by para-ring hydroxylation, carbamate hydrolysis, and side-chain oxidation. Chlorpropham is about 35% hydrolyzed in rats, whereas propham is hydrolyzed by a much smaller percent. The major urinary metabolites of

chlorpropham are 4-hydroxychlorpropham and 4-hydroxy-3-chloroaniline. Experience with p-aminophenol (see in index) suggests that the latter metabolite may oxidize hemoglobin to methemoglobin, but the possibility of methemoglobinemia has apparently not been investigated in poisoned animals. The parent compounds may cause local skin irritation, but are not skin sensitizers. Dermal absorption is not significant. Chlorpropham and propham are said to be oncogenic. If significant methemoglobinemia is demonstrable after an acute exposure, treat as for aniline poisoning (see latter in Section III).

Ref.: Assoc. of Amer. Pesticide Control Officials, 1966; Boyd and Carsky, 1969; Fang et al., 1974; Grunow et al., 1970; Larson et al., 1960; Worthing, 1979; Ryan, 1971; Spencer, 1973.

1230 Desmedipham 1230

Ethyl *m*-hydroxycarbanilate carbanilate, Ethyl 3-phenylcarbamoyloxyphenylcarbamate, Betanal, Betanex

Toxicity Rating: 3. Desmedipham, phenmedipham and phenmedipham-ethyl are post-emergence herbicides for use on beets to control broad-leafed weeds. The pure compounds have low acute oral toxicity to mammals (rat LD_{50} is 9.6 gm./kg. for desmedipham). Betanex, a 16% emulsifiable concentrate of desmedipham, is more toxic (rat LD_{50} is 3.7 gm./kg. active ingredient). A single oral dose of 2.5 gm./kg. of the formulation did not produce measurable inhibition of cholinesterase in the rat. Clinical signs and symptoms in poisoned laboratory animals, however, suggest that this enzyme may be significantly inhibited in vivo. For example, signs of oral intoxication include hypoactivity, salivation and muscle weakness. After inhalation exposure, salivation, nasal discharge, muscular weakness and labored breathing may occur. In rats, dogs and humans, desmedipham and phenmedipham are readily absorbed and rapidly hydrolyzed by plasma and liver esterases, yielding the corresponding alkyl-*N*-(3-hydroxyphenyl)carbamates and aniline (see in this index) or *m*-toluidine (in the case of phenmediphan). The carbamate moiety is further cleaved, yielding *m*-aminophenol and ultimately 3'-hydroxyacetanilid. Desmedipham is mildly irritating to skin and eyes. It is rapidly hydrolyzed in basic media and decomposes at high temperatures, releasing poisonous vapors. If signs and symptoms suggest cholinesterase inhibition, treat with atropine, as in carbaryl poisoning (see latter in Section III). If significant methemoglobinemia is demonstrable, treat as for aniline poisoning (see latter in Section III).

See also: Aniline, *Reference Congener in Section III.*
Ref.: NOR-AM Agricultural Products, date unknown; Worthing, 1979; Sonawane and Knowles, 1971.

1231 2,6-Di-*tert.*-butyl-*p*-tolyl-*N*-methylcarbamate 1231

Terbutol, e.g., Azak

Toxicity Rating: 1. Pre-emergence herbicide available as an 80% wettable powder. Oral LD_{50} as a 50% suspension in corn oil is greater than 35 gm./kg. in rats and in excess of 15 gm./kg. in dogs and cats. No deaths and no frank symptoms of poisoning were observed. Emesis occurred in about half the dogs, and the rats exhibited generalized inactivity. On intact or abraded rabbit skin 10 gm./kg. was tolerated with only slight and transient erythema. Moderate irritant in rabbit eye if unwashed but flushing with water after 1-min. exposures prevented the reaction. Slight to moderate erythematous and perhaps edematous reactions on human patch tests. Mice, rats and guinea pigs exposed to dust concentrations of 2800 mg./cu. m. for 4 hours showed no untoward reactions. Although relevant data were not located, there is a possibility that this compound has weak anticholinesterase activity; see Carbaryl in the index.

Ref.: Hercules Powder Co., 1962a.

1232 Karbutilate 1232

m-(3,3-Dimethylureido)phenyl *tert.*-butylcarbamate, e.g., Tandex

Toxicity Rating: 3. Carbamate herbicide used for soil sterilization on nonfood crop areas. Acute oral LD_{50} of technical grade material 3.0 gm./kg. in rats. Data suggest that it is not well absorbed through intact skin. Mild primary irritant in rabbit eye and on skin. May be a weak cholinesterase inhibitor, but an official of Niagara Chemical Division has stated that it does not inhibit cholinesterase. Treat symptoms of cholinesterase inhibition, if any, with atropine but avoid 2-PAM.

Ref.: Niagara Chemical Division, 1969.

Thiocarbamate herbicides

1233 Butylate 1233

S-Ethyl diisobutylthiocarbamate

Toxicity Rating: 3. A thiocarbamate herbicide, used to prevent germination of grass and weeds in maize, available in solubilized and granular forms. Low acute oral toxicity (rat LD_{50} 4 to 5 gm./kg.).