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CASWELL FILE

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ES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005934

JUN 12 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP 6F3417; Thiodicarb (LARVIN®) Petition for Tolerance for Almonds, Head Lettuce and Cole Crops

FROM: Alan C. Katz
Toxicology Branch/HED (TS-769)
Alan C Katz 6/4/87

TO: L. Schnaubelt/ D. Edwards, PM-12
Registration Division (TS-767)

THROUGH: M. vanGemert, Ph.D.
M. vanGemert 6/5/87
Head, Section III/Toxicology Branch/HED (TS-769)
and
T. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769)
Caswell # 900AA
6/12/87

ACTION REQUESTED:

A. Review 1-year feeding study in dogs and teratogenicity study in rabbits with thiodicarb technical material.

B. Union Carbide Agricultural Products Company, Inc. proposes that the following tolerances be established for the combined residues of thiodicarb (LARVIN®) and its toxic metabolite, methomyl, in or on:

Raw Agricultural Commodity	Proposed Tolerance, ppm
Almonds, nutmeat	2.0
Almonds, hulls	50.0
Broccoli	7.0
Cabbage	7.0
Cauliflower	7.0
Lettuce, head	25.0

RESPONSE:

A. New Data (See attached DER's, Appendix I)

1. Hamada, N.N. "One-Year Feeding Study in Dogs." Study No. 2100-126; Hazelton Laboratories America, Inc., Vienna, VA, for The Institute of Environmental Toxicology, Tokyo, Japan; submitted by Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC; dated April 16, 1986. EPA Accession No. 263018.

Dogs were given diet containing thiodicarb at levels calculated to be equivalent to mean doses of 0, 4.4, 12.8 and 38.3 mg/kg/day in males and 0, 4.5, 13.8 and 39.5 mg/kg/day in females. At the highest dose, thiodicarb caused slight reduction in mean total erythrocyte counts, hemoglobin and hematocrit levels and inhibition of plasma, RBC and brain cholinesterase activity. Reduced RBC cholinesterase activity was also found to be a potentially adverse treatment-related effect in mid-dose females. Relative (organ:body) weights of spleen and liver were significantly increased in the high dose female group, although no correlative histopathologic alterations were reported. Thus, the NOEL based on cholinesterase inhibition is approximately 4.5 mg/kg/day, while the NOEL for other effects is 12.8 mg/kg/day. The study is classified Core-Minimum.

2. Rodwell, D.E. "A Teratology Study in Rabbits with Thiodicarb"; Project No. WIL-95002 by Wil Research Laboratories, Inc., Ashland, OH, for Union Carbide Agricultural Products Company, Inc., Research Triangle Park, NC; dated May 16, 1986. Accession No. 263019.

This study provides limited evidence for establishing a NOEL for maternal toxicity at 20 mg/kg/day, based on minimal reduction in body weight gain and food consumption at the highest dose tested (40 mg/kg/day) during the first week of treatment. Data from rangefinding studies should be submitted to support the LOEL for maternal toxicity. The NOEL for developmental toxicity is at least 40 mg/kg/day; the LOEL could not be established. This study is classified Core-Supplementary and may be upgraded following submission and evaluation of rangefinding studies.

B. EIGHT-POINT SUMMARY

1. A Summary of Selected Toxicology Data Considered in Setting the Tolerance

Teratology - Rat	Teratogenic NOEL> 100 mg/kg/day (HDT) Fetotoxic NOEL = 3 mg/kg/day Maternal NOEL < 0.5 mg/kg/day
Teratology - Mouse	Teratogenic NOEL > 200 mg/kg/day (HDT) Fetotoxic NOEL > 200 mg/kg/day Maternal NOEL = 100 mg/kg
2-Year Feeding/Onco - Rat	Systemic NOEL = 3 mg/kg/day ChE NOEL $\geq$ 10 mg/kg/day (HDT) Oncogenic NOEL > 10 mg/kg/day
1-Year Feeding - Dog (new data)	Systemic NOEL = 12.8 mg/kg/day ChE NOEL = 4.5 mg/kg/day
2-Year Feeding/Onco - Mouse	Systemic NOEL = 3 mg/kg/day Onco NOEL > 10 mg/kg/day (HDT)
3-Gen. Repro - Rat	NOEL = 10 mg/kg/day (HDT)

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2. Summary of Toxicological Data Considered Desirable But Currently Lacking

The registrant is advised to submit data necessary for upgrading rabbit teratology study (Core-Supplementary).

3. Action Being Taken to Obtain the Lacking Information

The registrant is being informed through the Registration Division.

4. Summary of Other Tolerances Granted

Food Name	Tolerance (ppm)
Cottonseed oil	0.4
Cottonseed meal	0.4
Soybeans	0.2
Sweet corn	2.0

5. Summary of TMRC in Relation to ADI

Please refer to the attached computer printout (Appendix II).

The existing TMRC (0.0005 mg/kg/day) is equivalent to 1.8% of the PADI. The new tolerances will occupy 4.5% of the PADI, and the new TMRC (0.0019 mg/kg/day) will be 6.3% of the PADI.

6. Acceptable Daily Intake Data

The PADI is based on the 2-year feeding study in rats.

NOEL (mg/kg/day)	UF	PADI (mg/kg/day)	PMPI (mg/day), 60 kg
3	100	0.03	1.8

7. There are at this writing no pending regulatory actions against the registration of this pesticide.

8. There are currently no other relevant considerations in the setting of these tolerances.

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APPENDIX I.

DATA EVALUATION RECORDS

A

Reviewed by: Alan C. Katz Alan C Katz 6-1-87
Section 3, Tox. Branch (TS-769C)
Secondary reviewer: Marcia vanGemert, Ph.D. M. vanGemert 6/5/87
Section 3, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: Dog Chronic Feeding

TOX. CHEM. NO.: 900 AA

ACCESSION NUMBER: 263018

TOX. PROJECT NO.: 2195

TEST MATERIAL: Thiodicarb (Technical)

SYNONYMS: LARVIN

STUDY NUMBER(S): 2100-126

SPONSOR: The Institute of Environmental Toxicology, Tokyo, Japan

REGISTRANT: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

TESTING FACILITY: Hazleton Laboratories America, Inc., Vienna, VA

TITLE OF REPORT: "One-Year Feeding Study in Dogs"

AUTHOR (Study Director): N.N. Hamada

REPORT ISSUED: April 16, 1986

CONCLUSIONS:

Dogs were fed diet containing thiodicarb technical material at concentrations of 0, 164, 487 or 1506 ppm for 1 year; based upon food consumption and body weight determinations, mean dosage levels were calculated to be 0, 4.4, 12.8 and 38.3 mg/kg/day, respectively, for males and 0, 4.5, 13.8 and 39.5 mg/kg/day for females. At the highest dose, thiodicarb caused slight reduction in mean total erythrocyte counts, hemoglobin and hematocrit levels and inhibition of plasma, RBC and brain cholinesterase activity. Although no consistent statistically significant ChE inhibition was demonstrated in the low or mid dose groups, reduced RBC ChE activity in mid dose females was found to be a potentially adverse treatment-related effect. Relative (organ:body) weights of spleen and liver were significantly increased in the high dose female group, although no correlative histopathologic alterations were reported. Thus, the NOEL based on ChE inhibition is approximately 4.5 mg/kg/day, while the NOEL for other effects is 12.8 mg/kg/day.

Classification: Core-Minimum

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A. MATERIALS:

1. Test compound: Thiodicarb, technical; Description: White powder Ref. # HTS 4843AA, Purity 91.6%. Storage: frozen until used.

2. Test animals: Beagle dogs; Age: 29-33 weeks at initiation of study. Weight: males- 8.5 to 10.5 kg; females- 7.1 to 10.1 kg. Source: Hazleton Research Products, Inc., Denver, PA. Quarantine/Acclimation Period: 47 days.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Conc. in diet (ppm)	male	female
1 Cont.	0	6	6
2 Low (LDT)	164	6	6
3 Mid (MDT)	487	6	6
4 High(HDT)	1506	6	6

2. Diet preparation

Diet was prepared weekly (one week in advance of feeding). Feed was apparently stored at room temperature, as called for in the study protocol (but not specified in the final report). Samples of treated food were analyzed for concentration weekly during the initial four weeks of the study and at 4-week intervals after that. Stability for a 21-day period was determined prior to initiation of the study.

Results -

Stability: Data were presented from a dose rangefinding study in which the target levels for thiodicarb in the diet were 109.5 and 3155.3 ppm. These data showed no apparent reduction in test compound concentration in the diet at 21 days; however, conditions of storage were not specified for the blended feed used in the stability tests or in the chronic study.

Concentration/Homogeneity: Concentration and homogeneity were generally acceptable, except for the mid dose diet at 32 weeks (1 sample reported at 90.5% of target and the mean of 3 injections of a second sample reported at 76.4%).

3. Purina Certified Canine Diet No. 5007 was available for 2 hours daily and water was available ad libitum. On days when blood samples were collected for cholinesterase determination, except at 52 weeks, the food was available until after the sample collection was completed (reported as generally up to 4 hours of additional time).

4. Statistics - The following procedures were utilized in analyzing the numerical data:

   Tests for homogeneity of variances and ANOVA (one-tailed) and Dunnett's t-test (two-tailed). All statistical tests were evaluated at the 5% probability level.

5. Quality assurance was certified by Frederick G. Snyder, Director, Office of Quality Assurance (Hazleton). GLP compliance was assured by the study director, N. Nicki Hamada.

C. METHODS AND RESULTS

1. Observations

Animals were inspected once daily for signs of toxicity and twice daily for mortality and moribundity.

Toxicity/Mortality (survival)

No animals died prior to termination of the study. No treatment-related clinical signs were apparent.

2. Body weight

Animals were weighed weekly throughout the study.

No treatment-related body weight differences were found.

3. Food and water consumption; compound intake

Food, water and test compound consumption were determined. Food efficiency was not calculated.

Mean test compound consumption was calculated to be 4.4, 12.8 and 38.3 mg/kg/day in low, mid and high dose males, respectively; values for females were 4.5, 13.8 and 39.5 mg/kg/day.

Water consumption in the treated groups was comparable to that of the controls throughout the study.

Statistically significant reductions (compared to controls) in mean weekly food consumption occurred sporadically in mid and high dose males. Analysis of total food consumption over the 52-week period, however, showed no significant treatment-related differences.

4. Ophthalmological examinations

Performed on all animals prior to initiation of treatment and at week 52. Pupils were dilated using Tropicamide ophthalmic solution (1% Mydriacyl®, Alcon Laboratories, Inc.). Observations were made using an indirect ophthalmoscope and a slit lamp.

No treatment-related ocular changes were found.

5. Blood was collected before treatment and at 13, 26 and 52 weeks for hematology and routine clinical analysis from all animals.

Samples for cholinesterase determinations were collected prior to initiation (weeks -6, -4 and -3), at week 5 and at 13, 26 and 52 weeks. For the cholinesterase determinations, dogs were allowed access to feed until the time of sample collection, except for inadvertent withdrawal of food approximately 4 hours prior to blood collection at 52 weeks.

The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*		Mean corpuscular HGB conc.(MCHC)
x	Erythrocyte count (RBC)*		Mean corpuscular volume (MCV)
x	Platelet count*		Reticulocyte count
	Blood Clotting Measurements	x	Heinz bodies
	(Thromboplastin time)		
x	(Clotting time)		
x	(Prothrombin time)		

* Required for subchronic and chronic studies

As shown in Table 1, slightly reduced mean erythrocyte counts, hemoglobin and hematocrit levels were found in high dose male and female groups at 13, 26 and 52 weeks; the differences in these mean hematologic values were found to be statistically significant only with respect to the erythrocyte counts and hemoglobin levels in high dose males at 13 and 26 weeks.

b. Clinical Chemistry

X	Electrolytes:	X	Other:
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine* (week 52 only)
	Magnesium*	x	Blood urea nitrogen*
x	Phosphorous*	x	Cholesterol*
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
	Enzymes	x	Total Bilirubin*
x	Alkaline phosphatase	x	Total Serum Protein*
x	Cholinesterase#		Triglycerides
x	Creatine phosphokinase*		Serum protein electrophoresis
x	Lactate dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
x	gamma glutamyl transferase	x	Methemoglobin
	glutamate dehydrogenase	x	Direct bilirubin (weeks 13, 26 and 52)

* Required
\# Should be required for OP

As shown in Table 2, plasma cholinesterase activity was significantly reduced in high dose males and females at 5, 13 and 26 weeks, and in low and mid dose females at 13 weeks. Significant reductions in RBC cholinesterase were found at 5 weeks in high dose females, at 13 weeks in high dose males and mid and high dose females, and at 26 weeks in high dose females. Brain cholinesterase activity was reduced in high dose males (32% inhibition compared to control mean) and females (28% inhibition).

Differences in other group mean blood analyte values occurred sporadically and did not appear to be treatment-related. Increased mean alanine aminotransferase values in mid and high dose males at 52 weeks were attributable to elevated levels in 2 dogs in each of these groups.

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6. Urinalysis

Urine was collected from water fasted animals at prior to treatment (week -6) and at 13, 26 and 52 weeks.

The CHECKED (X) parameters were examined.

X		X	
x	Appearance*	x	Glucose*
x	Volume* (overnight)	x	Ketones*
x	Specific gravity*	x	Bilirubin*
x	pH	x	Blood*
x	Sediment (microscopic)*		Nitrate
x	Protein* (albumin)	x	Urobilinogen
		x	Reducing substances

* Required for chronic studies
° Not required for subchronic studies

Urinalysis results showed no evidence of a treatment-related effect.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

The tissues were preserved in 10% neutral buffered formalin, embedded in Paraplast®, and stained with H & E.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	x	.Aorta*	xx	.Brain*†
x	.Salivary glands*	xx	.Heart*	x	Periph. nerve*(sciatic)
x	.Esophagus*	x	.Bone marrow*	x	Spinal cord (3 levels)*
x	.Stomach*	x	.Lymph nodes*	x	.Pituitary*
x	.Duodenum*	x	.Spleen*	x	Eyes *
x	.Jejunum*	x	.Thymus*		Glandular
x	.Ileum*		Urogenital	xx	.Adrenals*
x	.Cecum*	xx	.Kidneys*†		Lacrimal gland
x	.Colon*	x	.Urinary bladder*	x	Mammary gland*
x	.Rectum*	xx	.Testes*†	x	.Parathyroids*†
xx	.Liver*†	x	Epididymides	x	.Thyroids*†
x	Gall bladder*	x	Prostate		Other
x	.Pancreas*		Seminal vesicle	x	Bone*(sternum)
	Respiratory	xx	Ovaries*†	x	Skeletal muscle*
x	.Trachea*	x	.Uterus*/cervix	x	Skin*
x	.Lung*	x	Vagina	x	All gross lesions and masses*

* Required
† Organ weights required

Testes were weighed with epididymides. Liver was weighed with gallbladder drained. Thyroid and parathyroid were weighed together. Brain weights included brain stem.

a. Organ weight

Organ weight data are summarized in Table 3. There were no statistically significant differences between treated groups and controls with respect to mean absolute organ weights or organ:brain weight ratios, although these values for spleen and liver in female treated groups showed slight dose-related increases. Relative to body weight, values for these organs were significantly increased ($p \leq 0.05$) in the high dose females. No other treatment-related effects on organ weights were found.

b. Gross pathology

Gross observations at necropsy revealed no apparent treatment-related effects.

c. Microscopic pathology

No treatment-related histopathologic alterations were apparent.

D. DISCUSSION:

Because of the relatively rapid reversibility of carbamate-induced cholinesterase (ChE) inhibition, a critical factor in evaluation of plasma and RBC cholinesterase inhibition is the time elapsed between administration of the test compound and collection of samples for analysis. In the case of thiodicarb, this is evident in the apparent "recovery" of plasma and RBC ChE levels in treated groups at 52 weeks which is presumed to be due to inadvertent withdrawal of dosed feed several hours prior to bleeding. Additional experimental evidence was provided in the present study, in which 2 high dose male dogs (Nos. 22998 and 22999) were serially bled (at the end of week 22) prior to feeding and 0, 2, 4 and 6 hours postfeeding, and plasma/RBC ChE results were compared. The data reported were as follows:

Interval	Plasma ChE (umol/g)		RBC ChE	
	No. 22998	No. 22999	No. 22998	No. 22999
Prefeeding	10.2	10.1	7.6	12.8
Postfeeding (hrs):				
0	6.6	6.3	3.2	4.2
2	6.9	6.4	4.4	5.7
4	7.5	6.9	5.9	8.1
6	8.5	8.0	8.4	10.8

Except for potential diurnal and analytical variability, these results indicate that the maximum ChE inhibitory response occurred within 2 hours of cessation of the feeding period. The feeding period itself was 2 hours' duration, and no specific indication was given as to when the dogs actually stopped eating. It may be further postulated that, since the dogs were conditioned to eat during a regularly scheduled 2-hour period, only minimal additional consumption may have occurred during the extended period of food accessibility on days of bleeding for ChE determinations during the chronic study. Since feed consumption was reported on a weekly rather than daily basis, this reviewer cannot evaluate the effect of extended availability in terms of additional consumption. Also, assuming all dogs could not have been bled simultaneously, it is questionable as to whether the durations of these postprandial "lag" periods may have differed significantly between groups.

It is this reviewer's opinion that, based on the data shown in Table 2, thiodicarb caused potentially significant inhibition of ChE activity not only in the high dose group (i.e., plasma, RBC and brain levels in both sexes) but also in the mid dose group (i.e., particularly with respect to RBC levels in females).

TABLE 1. Selected Hematological Determinations in Dogs Fed Thiodicarb for One Year

(excerpted from study report)

GROUP AND DOSAGE LEVEL		RBC MI/UL WEEK -6	RBC MI/UL WEEK 13	RBC MI/UL WEEK 26	RBC MI/UL WEEK 52	HGB G/DL WEEK -6FM	HGB G/DL WEEK 13	HGB G/DL WEEK 26	HGB G/DL WEEK 52	HCT % WEEK -6	HCT % WEEK 13	HCT % WEEK 26	HCT % WEEK 52
						MALE							
1	MEAN	6.90	6.95	6.86	6.92	15.7	15.6	15.4	15.8	45.4	45.8	45.2	45.1
0 PPM	S.D.	.603	.665	.665	.741	1.37	1.40	1.40	1.51	3.95	4.35	4.20	4.44
	N	6	6	6	6	6	6	6	6	6	6	6	6
2	MEAN	6.33	6.26	6.56	6.70	14.4	14.3	14.9	15.4	41.6	41.5	43.2	44.0
164.0 PPM	S.D.	.607	.244	.323	.231	1.19	.46	.79	.59	3.44	1.49	2.39	1.69
	N	6	6	6	6	6	6	6	6	6	6	6	6
3	MEAN	6.53	6.42	6.39	6.41	15.1	14.8	14.7	14.8	43.1	43.3	42.6	42.2
487.1 PPM	S.D.	.584	.622	.564	.569	1.42	1.24	1.04	1.13	3.73	3.84	3.61	3.20
	N	6	6	6	6	6	6	6	6	6	6	6	6
4	MEAN	6.53	5.66 *	5.78*	6.13	14.7	13.4 *	13.4*	14.2	42.7	39.4	39.6	41.4
1505.8 PPM	S.D.	.280	.707	.591	.625	.51	1.36	.92	1.32	1.85	4.82	3.07	3.84
	N	6	6	6	6	6	6	6	6	6	6	6	6
						FEMALE							
1	MEAN	7.18	6.25	6.47	6.98	16.4	14.4	14.8	16.0	47.3	41.1	42.6	45.8
0 PPM	S.D.	.711	.925	1.092	.813	1.67	1.84	2.24	1.82	4.82	6.10	7.22	4.98
	N	6	6	6	6	6	6	6	6	6	6	6	6
2	MEAN	7.36	6.63	6.14	6.51	17.0	15.4	14.3	15.2	49.4	44.3	41.0	43.0
164.0 PPM	S.D.	.317	.787	.536	.774	.39	1.37	1.28	1.30	1.26	4.44	3.92	3.60
	N	6	6	6	6	6	6	6	6	6	6	6	6
3	MEAN	7.27	6.59	6.29	6.40	16.7	15.5	14.8	15.0	48.2	44.9	42.3	42.8
487.1 PPM	S.D.	.629	.815	.986	.955	1.38	1.83	2.06	2.00	3.97	5.46	6.40	5.82
	N	6	6	6	6	6	6	6	6	6	6	6	6
4	MEAN	7.42	5.58	5.68	5.68	16.5	13.4	13.6	13.4	47.9	39.0	39.2	39.1
1505.8 PPM	S.D.	.408	.783	.412	.731	.65	1.55	1.01	1.50	1.66	5.44	3.22	4.33
	N	6	6	6	6	6	6	6	6	6	6	6	6

* Significantly ($p \leq 0.05$) different from control mean.

TABLE 2. Cholinesterase Activity in Dogs Fed Thiodicarb For One Year

Dietary Level (ppm)	Plasma Cholinesterase Level[a] at Week -3	5	13	26	52[b]	Brain Cholinesterase 52 weeks
Males						
0	(10.4)	(9.9)	(9.9)	(9.2)	(9.1)	(7.5)
164	90	83	84	80	80	107
487	97	85	83	89	99	96
1506	97	68*	72*	71*	90	68*
Females						
0	(10.3)	(10.4)	(11.0)	(10.3)	(10.0)	(8.2)
164	94	88	82*	89	96	106
487	103	90	82*	90	102	98
1506	95	63*	67*	70*	93	72*
	RBC Cholinesterase					
Males						
0	(8.6)	(7.6)	(8.9)	(8.2)	(9.0)	
164	106	101	87	95	97	
487	107	88	73	94	91	
1506	107	67	55*	79	82	
Females						
0	(9.1)	(8.7)	(9.3)	(9.3)	(9.2)	
164	107	93	95	86	105	
487	101	76	72*	82	99	
1506	99	59*	57*	68*	102	

a- Control mean values, in parentheses, expressed in umol/g; values for treatment groups are given in percent relative to respective control value. Number of animals in each group = 6.

b- Food removed approximately 4 hours prior to blood collection.

*- Significantly ($p \leq 0.05$) different from control mean value.

TABLE 3. Selected Organ Weight Data[a]

Dietary Level (ppm)		Absolute Weight (g) Body	Liver	Spleen	Relative Weight (Organ:Body) Liver[b]	Spleen
Males						
0	Mean	10050	239	22.3	2.4	0.22
	SD	857	51	4.9	0.3	0.04
164	Mean	10467	256	22.9	2.5	0.22
	SD	493	26	1.8	0.3	0.01
487	Mean	9967	236	22.1	2.4	0.22
	SD	689	15	5.0	0.1	0.04
1506	Mean	10133	254	23.9	2.5	0.24
	SD	1417	51	3.1	0.2	0.03
Females						
0	Mean	9633	238	20.8	2.5	0.21
	SD	1398	37	8.0	0.2	0.06
164	Mean	9183	261	23.8	2.8	0.26
	SD	995	41	6.9	0.3	0.08
487	Mean	9967	288	26.2	2.9	0.26
	SD	792	32	4.2	0.3	0.03
1506	Mean	9483	290	31.4	3.1*	0.33*
	SD	1083	50	7.3	0.4	0.07

a n= 6/sex/group

b Drained gallbladder weighed with liver

* Significantly ($p \leq 0.05$) different from control mean

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

005934

EPA: 68-02-4225
DYNAMAC No. 240A
May 22, 1987

DATA EVALUATION RECORD

THIODICARB

Teratogenicity Study in Rabbits

STUDY IDENTIFICATION: Rodwell, D. E. A teratology study in rabbits with thiodicarb (project No. WIL-95002 by Wil Research Laboratories, Inc., Ashland, OH, for Union Carbide Agricultural Products Company, Inc., Research Triangle Park, NC; dated May 16, 1986.) Accession No. 263019.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 5-22-87

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1. CHEMICAL: Thiodicarb insecticide; Larvin; UC51762; dimethyl NN' thiobis (methylimino) carbonyloxy bis ethanimidothioate; ethanimidothioic acid; HTS 5833 AA.

2. TEST MATERIAL: Thiodicarb technical was described as a white powder containing 93% active ingredient.

3. STUDY/ACTION TYPE: Teratogenicity study in rabbits.

4. STUDY IDENTIFICATION: Rodwell, D. E. A teratology study in rabbits with thiodicarb (project No. WIL-95002 by Wil Research Laboratories, Inc., Ashland, OH, for Union Carbide Agricultural Products Company, Inc., Research Triangle Park, NC; dated May 16, 1986.) Accession No. 263019.

5. REVIEWED BY:

Guillermo Millicovsky, Ph.D.
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Date: 5/22/87

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Alan Katz, M.S., D.A.B.T.
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Signature: Alan Katz
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Marcia Van Gemert, Ph.D.
EPA Section Head

Signature: M. VanGemert
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7. CONCLUSIONS:

A. This study provides some evidence for establishing a NOEL for maternal toxicity at 20 mg/kg/day based on minimal (but statistically significant) reduction in body weight gain and food intake reported at 40 mg/kg/day during the first week of treatment. Data from rangefinding studies should be submitted to support the LOEL for maternal toxicity. We assess that the NOEL for developmental toxicity is at least 40 mg/kg/day, the highest dose tested in this study; the LOEL could not be established.

B. This study is classified Core Supplementary, and may be upgraded following submission and evaluation of rangefinding studies.

Item 8--see footnote 1.

9. BACKGROUND: Dose levels for this study were reportedly based on two dose rangefinding studies (WIL-95001) with pregnant rabbits dosed at 25, 50, 125, 250, and 500 mg/kg/day and 1, 5, 10, 20, and 40 mg/kg/day. The results of these studies were apparently not submitted for EPA review.

Item 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Materials: Thiodicarb technical was mixed daily with 0.5% aqueous methylcellulose to produce test mixture concentrations of 0, 5, 20, and 40 mg/mL. The dosing mixtures were administered by gavage at a volume of 1 mL/kg/body weight; the dosage levels were 0 (control), 5, 20, and 40 mg/kg/day.

2. Test Animals and Experimental Methods: Sexually mature, virgin female New Zealand White rabbits were obtained from Hazleton-Dutchland, Inc., Pennsylvania. Upon arrival, these animals were weighed, examined, individually housed, and then acclimated for at least 30 days. Environmental controls in animal rooms were set at 67±3°F, 40% minimum relative humidity, and a 12-hour light/12-hour dark photoperiod. Temperature and relative humidity deviated slightly and the author reported that these deviations did not negatively affect the validity of the study; actual temperature and

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[1]Only items applicable to this DER were included.

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humidity values were not reported. Animals were provided with food and water ad libitum during the study; however, only 150 g/day of diet were available to each animal during the acclimation period.

Following the acclimation period, animals considered to be in acceptable health and weighing approximately 3-5 kg were randomly selected, artificially inseminated, and injected with human chorionic gonadotropin; the day of insemination was designated gestation day (GD) 0. A total of 22 inseminated females were randomly assigned to each of the four study groups.

Females were weighed on GD 0, 6, 12, 19, 24, and 29, and dosed on GDs 6-19; dosages were based on the most recently obtained individual body weights.

All surviving females were killed (by injection of T-61® euthanasia solution) on GD 29 and subjected to thoracic and abdominal necropsy. The number of corpora lutea was recorded. Gravid uteri were weighed and examined. The number, location, and status of implantation sites were determined. The pregnancy status of uteri with no gross evidence of implantation was determined by immersion in 10% ammonium sulfide solution.

Viable fetuses were weighed and examined for gross external abnormalities. Late resorptions were measured (crown-rump length) and discarded. Fetuses were examined for visceral abnormalities by a modification of the method described by Staples and internally sexed. Brains were examined through a midcoronal section. Eviscerated fetuses were skinned, fixed, and stained with Alizarin Red S for skeletal examination.

Mean maternal body weight, body weight gain, food consumption, fetal weight, number of corpora lutea, implantations, and fetuses were analyzed by ANOVA and Dunnett's test. The number of litters with variations and malformations were compared by Fisher's exact test. The number of resorptions and dead fetuses were compared by the Mann-Whitney U-test. Fetal sex ratios were compared by Chi-square test with Yates' correction factor.

12. REPORTED RESULTS:

A. Test Material: The methods used for chemical analyses of dosing preparations were apparently validated using a reference standard (HTC 3801 AA) of 97.66% purity. Results of these analyses indicate that the concentration and homogeneity of the preparations were acceptable.

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B. Maternal Effects: One female from the 20-mg/kg/day group died on GD 17; three females in the 40-mg/kg/day group died on GD 14, 17, and 19, respectively. Necropsy findings for these animals suggest that their deaths were caused by aspiration of the dosing preparations, and not a result of compound-related effects. Maternal clinical signs for the dosed groups were comparable with controls. The author noted various signs (including hair loss, soft stool, decreased defecation, etc.) in females from all groups. One control female aborted on GD 22; no other abortions were reported.

Maternal body weights for the 5- and 20-mg/kg/day groups were comparable with controls; however, body weights for the 40-mg/kg/day group were slightly (but not significantly) reduced from GD 6-29 (Table 1). The body weight values for this group were affected by a 637 g body weight loss in animal No. 3901; this animal had fatty liver changes not noted in other animals in this group. Animal No. 3890, also in this group lost 393 g during GD 6-29; this animal showed evidence of non-lethal aspiration of dosing mixture, enlarged heart, and white nodules on lungs observed at necropsy. Body weight gains for females in this group were also reduced (significantly for GD 6-12) when compared with controls (Table 1).

Food consumption changes were consistent with the effects on body weight; food intake for animals in the 40-mg/kg/day group was reduced when compared with controls (significantly during GD 6-12) after the initiation of dosing (Table 2). Food consumption for the 5- and 20-mg/kg/day groups was comparable to that of controls.

No compound-related effects were evident from necropsy findings of surviving females in the dosed groups.

C. Developmental Effects: Gravid uterine weights showed a mild, progressive decline with increasing dose (Table 3); however, none of the values were significantly different from control. No adverse compound-related effects were noted for the numbers of corpora lutea, resorptions, implantations, and viable and dead fetuses. The percentage of male fetuses was comparable among all groups.

Fetal body weights at 5 and 20 mg/kg/day were comparable with controls; however, body weights were slightly (but not significantly) reduced at 40 mg/kg/day when compared with controls. The author stated that the group mean fetal body for the 40-mg/kg/day group was comparable to their historical control value.

No external, visceral, or skeletal malformations were reported for fetuses in the 40-mg/kg/day group (Table 3). Malformations (brachydactyly, adactyly, hydrocephaly, and skull, rib, and vertebral malformations, etc.) noted for fetuses in the control and 5- and 20-mg/kg/day groups were considered incidental. No compound-related effects were reported for the incidence or type of developmental variations.

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TABLE 1. Effects of Thiodicarb on Maternal Body Weight and Body Weight Changes in Rabbits

Gestation Day	Study Event	Dosage (mg/kg/day) 0	5	20	40
		Mean Body Weight (g±SD)			
0	Insemination	3796±314	3702±289	3757±288	3724±322
6	Start Dosing	3863±329	3816±259	3837±320	3787±299
12		3957±326	3930±273	3934±318	3816±330
19		4047±336	4015±272	4021±323	3877±402
29	Termination	4117±464	4092±306	4189±375	3896±446

Gestation Days	Study Period	Dosage (mg/kg/day) 0	5	20	40
		Mean Body Weight Change (g±SD)			
0-6	Predosing	67±166	114±133	81±127	63±141
6-12		94±63	114±58	97±79	29±85*
6-19	Dosing	185±92	199±116	211±104	113±169
19-29	Postdosing	82±210	78±153	168±141	-20±192
0-29	Gestation	342±269	390±240	446±213	184±361

*Significantly different from control value ($p \leq 0.05$).

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TABLE 2. Effects of Thiodicarb on Mean Maternal Food Consumption in Rabbits (g/kg/day)

Gestation Day	Dosage (mg/kg/day) 0	5	20	40
0-6	37±10	34±7	33±7	33±8
6-12	46±5	47±4	45±5	41±5*
6-19	43±6	43±7	43±5	39±8
19-29	28±10	30±8	33±7	25±12
0-29	36±6	36±6	37±5	33±8

*Significantly different from control value ($p \leq 0.05$).

TABLE 3. Effects of Thiodicarb on Developmental Parameters in Rabbits

	Dosage (mg/kg/day)			
	0	5	20	40
No. females				
Inseminated	22	22	22	22
Aborted	1	0	0	0
Died	0	0	1	3
Nongravid	3	1	0	4
With resorptions only	0	1	1	0
No. litters examined	18	21	21	15
Mean per litter				
No. corpora lutea	10.7	10.8	10.7	11.3
No. implantations	8.1	8.3	7.0	7.5
No. viable fetuses	7.7	7.5	6.5	6.9
No. dead fetuses	0.0	0.0	0.0	0.0
No. early resorptions	0.2	0.5	0.4	0.5
No. late resorptions	0.1	0.2	0.0	0.1
% Postimplantation loss[a]	5.3	13.0	10.4	8.1
% Male fetuses[a]	45.4	43.6	42.6	42.9
Gravid uterine weight (g)	466.5	440.9	400.7	387.2
Fetal body weight (g)	42.7	41.8	44.0	39.6
External malformations				
% Fetuses affected	0.7	0.6	0.0	0.0
% Litters affected	5.6	5.0	0.0	0.0
Visceral malformations				
% Fetuses affected	0.0	0.0	2.2	0.0
% Litters affected	0.0	0.0	15.0	0.0
Skeletal malformations				
% Fetuses affected	1.4	2.5	3.6	0.0
% Litters affected	11.1	20.0	20.0	0.0

[a]Calculated by the reviewers from available data.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study author concluded that 40 mg/kg/day thiodicarb produced maternal toxicity. No evidence of embryo/fetotoxicity (including teratogenicity) was noted at 5, 20, or 40 mg/kg/day.

B. A quality assurance statement was signed and dated May 16, 1986.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Test Material: Results from chemical analysis of dose preparations indicate that the concentrations of the test material were acceptable for all dose levels; in addition, analyses of samples obtained at three different times during the study indicate that the preparations were homogeneous.

B. Maternal Effects: One female in the 20-mg/kg/day group and three females in the 40-mg/kg/day group died during the gestation period. Necropsy and histopathologic findings suggest that these deaths were related to the gavage procedure and not due to the test material. No compound-related effects on clinical signs or mortality were reported.

Minimal but statistically significant reductions in maternal body weight gain and food consumption during the first 5 days of dosing at 40 mg/kg/day may be indicative of compound-related effects. Data from rangefinding studies may be useful in substantiating this assessment. We assess that dosage levels of 5 and 20 mg/kg/day were not toxic to pregnant rabbits. Necropsy findings conducted at study termination (GD 29) were comparable for dosed groups and controls.

C. Developmental Effects: No compound-related effects were apparent on pregnancy rates, abortions, total litter resorptions, or the numbers of corpora lutea, implantations, resorptions, live fetuses, and fetal sex ratios.

We assess that mild, nonsignificant decreases in gravid uterine weight noted in the low-, mid-, and high-dose groups and the nonsignificant reduction in fetal body weight in the high-dose group were not indicative of compound-related toxicity.

No malformations were reported for fetuses in the 40-mg/kg/day group. Several external, visceral, and skeletal malformations (brachydactyly, adactyly, cardiac and/or great vessel malformations, hydrocephaly, and rib, skull, and vertebral malformations, etc.) were reported for the 0-, 5-, and 20-mg/kg/day groups. The fetal and litter incidences of several of these findings (heart and/or great vessel, rib, and skull malformations) appear to be elevated at 20 mg/kg/day; however, the absence of similar findings at 40 mg/kg/day suggest that these effects may not necessarily be compound related.

No external variations were reported for fetuses in any dose group. Several visceral and skeletal variations were noted at all levels, but no clear pattern of dose relationship was apparent; therefore, we assess that these findings were incidental.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 4-11.

APPENDIX A

Materials and Methods

Thiodicarb

Page_____ is not included in this copy.

Pages 28 through 34 are not included.

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.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

APPENDIX II.

TOLERANCE ASSESSMENT SYSTEM SUMMARY REPORT

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Thiodicarb (Larvin) Caswell #900AA CAS No. 59669-26-0 A.I. CODE: 114501 CFR No. 180.407	2yr feeding- rat NOEL= 3.0000 mg/kg 0.00 ppm LEL= 10.0000 mg/kg 0.00 ppm ONCO: Negative- 2 species	Decreased body weight gain- males and females. No evidence of oncogenicity in rats or mice.	PADI 100 OPP RfD= 0.030000 EPA RfD= 0.000000 WHO RfD 0.030000 Type: ADI	Reproduction (Core-Supplementary)	TOX complete 11/19/86. WHO last reviewed 1986.

LISTING OF EXPOSURE BY RAC FOR: U.S. POPULATION - 48 STATES

FOOD CODE	FOOD NAME	TOLERANCE (PPM) NEW	TOLERANCE (PPM) APPROVED	TOLERANCE (PPM) PUBLISHED	EXISTING TOLERANCES TMRC (UG/KG/DAY)	EXISTING TOLERANCES %RfD	EFFECT OF NEW TOLERANCES NEW TMRC (UG/KG/DAY)	EFFECT OF NEW TOLERANCES NEW %RFD
27003OA	COTTONSEED-OIL			0.4000	0.0082	0.0272		
27003WA	COTTONSEED-MEAL			0.4000	0.0000	0.0002		
	CROP GROUP TOTALS FOR UNSPECIFIED:				0.0082	0.0274		
13020AA	LETTUCE-UNSPECIFIED	25.0000					0.2300	0.7667
	CROP GROUP TOTALS FOR LEAFY VEGETABLES (EXCL. BRASSICAE):				0.0000	0.0000	0.2300	0.7667
13005AA	BROCCOLI	7.0000					0.3439	1.1464
13007AA	CABBAGE-GREEN AND RED	7.0000					0.6555	2.1849
13008AA	CAULIFLOWER	7.0000					0.1109	0.3695
	CROP GROUP TOTALS FOR BRASSICA (COLE) LEAFY VEGETABLES:				0.0000	0.0000	1.1102	3.7008
15029AA	SOYBEANS-SPROUTED SEEDS			0.2000	0.0000	0.0000		
27010OA	SOYBEANS-OIL			0.2000	0.0644	0.2148		
28023AA	SOYBEANS-UNSPECIFIED			0.2000	0.0001	0.0003		
28023AB	SOYBEANS-MATURE/SEEDS DRY			0.2000	0.0002	0.0006		
28023WA	SOYBEANS-FLOUR/FULL FAT			0.2000	0.0006	0.0019		
28023WB	SOYBEANS-FLOUR/LOW FAT			0.2000	0.0002	0.0006		
28023WC	SOYBEANS-FLOUR/DEFATTED			0.2000	0.0025	0.0083		
	CROP GROUP TOTALS FOR LEGUME VEGETABLES:				0.0680	0.2266		
15005AA	CORN/SWEET			2.0000	0.4734	1.5780		
	CROP GROUP TOTALS FOR CEREAL GRAINS:				0.4734	1.5780		
03001AA	ALMONDS	2.0000					0.0056	0.0187
	CROP GROUP TOTALS FOR TREE NUTS:				0.0000	0.0000	0.0056	0.0187

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TOLERANCE ASSESSMENT SUMMARY FOR Thiodicarb (Larvin) DATE: 05/26/87
CASWELL #900AA

EXISTING TOLERANCES (PUBLISHED AND APPROVED) RESULT IN A TMRC OF:	0.0005	MG/KG/DAY
THE EXISTING TMRC IS EQUIVALENT TO:	1.8320	% OF THE ADI
PROPOSED NEW TOLERANCES RESULT IN A TMRC OF:	0.0013	MG/KG/DAY
THESE NEW TOLERANCES WILL OCCUPY:	4.4862	% OF THE ADI
IF THE NEW TOLERANCES ARE APPROVED, THE RESULTANT TMRC WILL BE:	0.0019	MG/KG/DAY
THE NEW TMRC WILL OCCUPY	6.3183	% OF THE ADI.