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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

FEB 26 1987

005743

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: I.D. # 100-530: Methidathion: Chronic oncogenic study in rats.

Tox. Chem. No. 378B
Accession #s 263322-26

TO: D. Edwards (PM 12)
Registration Division (TS-767C)

FROM: Marion P. Copley, D.V.M.,D.A.B.T. MPCopley 2/4/87
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Judith Hauswirth, Ph.D., Acting Section Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C) Judith W. Hauswirth 2/4/87
Melanie BB 2/26/87

In accordance with requirements from the Registration Standard on methidathion, Ciba-Geigy has submitted a 2-year dietary oncogenicity study in rats. The data evaluation review (DER) by Toxicology Branch (TB), is attached.

CONCLUSIONS: The 2-year rat dietary oncogenicity study (study number MIN 832001) is classified CORE-GUIDELINE and satisfies the regulatory requirement for 1 chronic/oncogenicity feeding study in rodents.

The systemic no-observable-effect-level (NOEL) = 4 ppm (0.2 mg/kg/day*) and the lowest effect level (LEL) = 40 ppm (2 mg/kg/day*) based on: signs of cholinesterase inhibition including reduced serum, RBC and brain cholinesterase; alopecia; and neurologic signs. The above mentioned lesions also occurred at 100 ppm (5 mg/kg/day*) along with decreased body weight gain and water consumption; increased food consumption; inflammatory skin lesions and focal accumulations of foamy macrophages in the lungs. There was no indication of oncogenic potential at any dose level.

The MTD of 100 ppm based on depressed water consumption and female body weight gain. High dose females weighed from 12 to 21 % less control values.

There are no special review concerns due to this study.

* see Appraisal of the Safety of Chemicals in Feeds, Drugs and Cosmetics, for the conversion factor.

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BACKGROUND:

1. The Registration Standard for Methidathion was completed in January 1983. It identified the following data gaps which were to be completed by Ciba-Geigy Corp. before January 13, 1987:

    - Teratology - second species
    - Reproduction - one species
    - Oncogenicity - two species[1,2]

2. This standard identified an unacceptable mouse oncogenicity study (I.B.T.) that suggested oncogenic potential.

3. There are currently no existing regulatory actions against registration and no special review is in progress.

NOTE TO THE PM:

In 1986, Ciba-Geigy submitted a mouse oncogenicity study (IRDC study 382-087) as required by FIFRA 6(a)(2) (see TB memorandum dated April 23,1986, from M. Copley to L. Schnaubelt). In the TB memo it was requested that the company submit mouse historical control data for liver tumors from the testing laboratory for approximately 2 years prior and subsequent to the study. The test species should be the same strain as used in the 2 year mouse study. The data should be presented by study and should separate the benign and malignant hepatocellular tumors as well as give a combined incidence. This information is necessary to completely evaluate the study and is also required for the TB Peer Review process.

[1] The mouse oncogenicity study is currently under review by TB
[2] The rat study is presented in this action

Copley, disc 11/11/16,Methidathion,# 378B,proj.2002,Ln 124,2/2//4/87

Reviewed by: Marion Copley, DVM, DABT 2/4/87
Section VI, Tox. Branch (TS-769C)
Secondary reviewer: Judith Hauswirth, PhD Judith Hauswirth 2/4/87
Section VI, Tox. Branch (TS-769C)

DATA EVALUATION REPORT 005743

STUDY TYPE: Chronic/onco feeding - rat TOX. CHEM. NO.: 378B

ACCESSION NUMBER: 263322-6

TEST MATERIAL: methidathion

STUDY NUMBER(S): MIN 832001

SPONSOR: Ciba-Geigy Corporation

TESTING FACILITY: Res. Dept, Pharmaceutical Div., Ciba-Geigy Corp., Summit, N.J.

TITLE OF REPORT: Methidathion 2-year oral oncogenicity and toxicity study in albino rats

AUTHOR(S): ET Yau, DN McMartin, IH Zaidi, and JD Green

REPORT ISSUED: 5/23/86

CONCLUSIONS:
Systemic NOEL = 4 ppm (0.2 mg/kg/day*)
LEL = 40 ppm (2 mg/kg/day*) based on: signs of cholinesterase inhibition including reduced serum, RBC and brain cholinesterase; alopecia; and neurologic signs. The above mentioned lesions also occurred at 100 ppm (5 mg/kg/day*) along with decreased body weight gain and water consumption; increased food consumption; inflammatory skin lesions and focal accumulations of foamy macrophages in the lungs. There was no indication of oncogenic potential at any dose level.
MTD = 100 ppm based on depressed water consumption and female body weight gain. High dose females weighed from 12 to 21 % less control values.

Classification: core-guideline

Special Review Criteria (40 CFR 154.7)

There are no special review concerns at this time.

* see Appraisal of the Safety of Chemicals in Feeds, Drugs and Cosmetics, for the conversion factor. Actual time weighted averages are in section C.3, Methods and Results, p. 4.

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A. MATERIALS:

1. Test compound: methidathion, Description Amber, solid, Batch #533131/M20244, Purity 97.3%

2. Test animals: Species: Rat, Strain: Sprague/Dawley[Crl:COBS®CD (SD)BR], Age: 5 weeks, Weight: 138.4-140.2 g (males), 111.9-114.5 g (females), Source: Ciba-Geigy AgChem Division, Greensboro, NC.

B. STUDY DESIGN:

1. Animal assignment (table 1 taken from the report)

Animals were assigned randomly to the following groups:

Table 1

METHIDATHION: 2-YEAR ORAL ONCOGENICITY AND TOXICITY STUDY IN ALBINO RATS (MIN 832001)

Dose Groups						
Group No.	No. of Rats	Rat ID No.	Sex	Accession No.	Week of Scheduled Sacrifice	Dietary Concentration (ppm)
1	50[a]	1-50	M	35001-50	93, 104	Control (0)
	20[b]	51-70	M	35051-70	104	Control (0)
	10[c]	71-80	M	35071-80	52	Control (0)
2	50[a]	81-130	M	35081-130	93, 104	Low (4)
	20[b]	131-150	M	35131-150	104	Low (4)
	10[c]	151-160	M	35151-160	52	Low (4)
3	50[a]	161-210	M	35161-210	93, 104	Mid (40)
	20[b]	211-230	M	35211-230	104	Mid (40)
	10[c]	231-240	M	35231-240	52	Mid (40)
4	50[a]	241-290	M	35241-290	93, 104	High (100)
	20[b]	291-310	M	35291-310	104	High (100)
	10[c]	311-320	M	35311-320	52	High (100)
5	10[d]	321-330	M	---	Pre-dose	Baseline
1	50[a]	331-380	F	35331-380	93, 104	Control (0)
	20[b]	381-400	F	35381-400	104	Control (0)
	10[c]	401-410	F	35401-410	52	Control (0)
2	50[a]	411-460	F	35411-460	93, 104	Low (4)
	20[b]	461-480	F	35461-480	104	Low (4)
	10[c]	481-490	F	35481-490	52	Low (4)
3	50[a]	491-540	F	35491-540	93, 104	Mid (40)
	20[b]	541-560	F	35541-560	104	Mid (40)
	10[c]	561-570	F	35561-570	52	Mid (40)
4	50[a]	571-620	F	35571-620	93, 104	High (100)
	20[b]	621-640	F	35621-640	104	High (100)
	10[c]	641-650	F	35641-650	52	High (100)
5	10[d]	651-660	F	---	Pre-dose	Baseline

a: Oncogenicity Study Subgroup. 5 rats/sex/group were randomly selected for sacrifice on Week 93.

b: Clinical Laboratory Test Group. Tests were performed on 10 rats/sex/period.

c: Interim Sacrifice Subgroup.

d: Pre-dose Baseline Data. No necropsy or histopathology examinations were performed on these animals. They were sacrificed by exsanguinations and removed from the study.

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Table 2 represents the treatment and sacrifice groups:

Table 2

Test Group	Dose in diet (ppm)	Main Study 104 months male	Main Study 104 months female	Interim Sac. 93 months male	Interim Sac. 93 months female	Interim Sac. 52 months male	Interim Sac. 52 months female
1 Cont.	0	65	65	5	5	10	10
2 Low (LDT)	4	65	65	5	5	10	10
3 Mid (MDT)	40	65	65	5	5	10	10
4 High(HDT)	100	65	65	5	5	10	10

2. Diet preparation

Diet was prepared weekly and stored at room temperature. Samples of treated food were analyzed for homogeniety (top, middle and bottom) monthly. Stability and purity were also checked by the sponser.

Results - The concentration of methidathion in the three groups ranged from 91.5 to 107.3 % throughout the study. The only exceptions were weeks 1 and 5 when the high dose had about 85 % and week 69 when all three groups had about 45 to 50 percent of the theoretical concentration. The registrant could find no preparation errors to explain these deviaions.

3. Animals received food (Certified Purina rodent chow #5002) and water ad libitum.

4. Statistics - The procedures (taken from the report) utilized in analyzing the numerical data are attached as appendix 1.

5. A signed quality assurance statement was attached.

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C. METHODS AND RESULTS:

1. Observations - The rats were examined daily for signs of toxicity and mortality. Physical examinations were conducted biweekly.

Mortality (survival) - There were no treatment related effects on mortality in either males or females (table 3).

Table 3.

	Number of early deaths or moribund sacrifices (%)			
dose (ppm)	males		females	
0	N=80	45 (60)	N=80	38 (48)
4	"	44 (60)	"	40 (50)
40	"	39 (54)	"	35 (44)
100	"	41 (54)	"	35 (44)

Toxicity (clinical signs) - Treatment and dose related effects included alopecia (males and females) at the mid and high doses after about 1 year, chromorhinorrhea (males and females) at the high dose and fasiculation in about 6 % of the high dose females. Other neurologic signs at the mid and high doses, including hypersensitivity to touch (females), and tremors(both sexes), appeared early in the study and decreased in intensity as the study progressed.

2. Body weight - Animals were weighed weekly for 12 weeks, then once every 4 weeks till term.

Treatment with methidathion resulted in a reduction* in body weight (<10 %) in the high dose males, when compared to controls, from weeks 1 to 16 and 92 to 100 and a reduction* of 10 to 13 % during weeks 72 to 92. There was a transient reduction* (<10 %) in the male mid dose weight until week 11. Body weight in the high dose females was reduced* 12 to 21 % throughout the study. Minimal reductions in the mid and low dose females were noted only during the first 3 weeks of study.

3. Food consumption and compound intake - Consumption was determined weekly for 12 weeks, then once every 4 weeks till term. Water consumption was measured only in 10 rats/sex/group at the same time points. Efficiency was not calculated. Time weighted averages of compound intake were determined using the known doses and body weight gain data.

* $p \leq 0.01$ when compared to controls

Food consumption - Throughout most of the study, food consumption was slightly (less than 10 %) but statistically ($p \leq 0.01$) increased in the mid dose males and to a greater extent, in the high dose males. Although there was also a periodic statistical increase in food consumption in the mid and high dose females it was minimal.

Food efficiency - Although efficiency was not calculated, the registrant suggested that it was decreased in the high dose and possibly mid dose males and females.

Compound intake - The time weighted averages for the 3 treatment groups were 0.16, 1.72 and 4.91 mg/kg/day for males and 0.22, 2.20 and 6.93 mg/kg/day for the females in the low, mid and high dose groups, respectively.

Water consumption - As can be seen in table 6, water consumption was not significantly decreased in the males. The high dose females, however, had a 20 to 40 % decrease throughout most of the study (weeks 2 to 98).

4. Ophthalmalogical examinations - Performed on all animals during weeks 51 and 104.

The registrant considered all ocular changes to be unrelated to treatment since they occurred sporadically in all groups. Eye lesions included corneal opacities and stippling, with lens and retinal alterations.

5. Blood was collected from 10 rats/sex (rats not used in the study) before treatment and from 10/sex/group at weeks 26, 52 (20/sex/group) 78, 93 (5/sex/group) and 104 for hematology and clinical analysis. Animals were fasted (overnight) prior to testing. RBC Cholinesterase activity was measured in duplicate. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*[1]
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*	X	Reticulocyte count (control and high doses)
	Blood Clotting Measurements		
	(Thromboplastin time)		
X	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies
1 performed on all rats at week 104

Results - As can be seen in table 4, there were statistically significant changes in several hematology parameters in the high dose group. These included a decreased HGB and RBC in females and decreased HCT in both sexes. Since these changes were often sporadic and were within the normal ranges for rats, it is unlikely that they were treatment related. The slight increase in platelets and the reversal of the neutrophil:lymphocyte ratio in both sexes, also at the high dose, were probably treatment related. A slight increase in absolute neutrophil count was responsible for the latter shift.

Table 4 Select hematology parameters

		males						females					
	Week	0	26	52	78	98	104	0	26	52	78	98	104
Test	PPM	N 10	10	20	10	5	10	10	10	20	10	5	10
HGB	0							14.45	14.94††	14.75††	14.69††	15.04	13.40
(Gm/Dl)	4								15.75	15.35	15.10	14.74	13.53
	40		NO SIGNIFICANT CHANGES						15.35	14.66	14.92	14.15	13.21
	100								14.10**	13.55**	13.50**	14.98	11.55
RBC	0							5.92	7.37	6.98†	6.96	6.52	5.71
X 10^6	4		NO SIGNIFICANT CHANGES						7.71	7.28	7.38	6.30	5.87
	40								7.76	7.20	7.36	6.25	5.91
	100								7.20	6.51*	6.83	6.86	5.28
HCT	0	42.6	46.1	45.3	44.3†	40.0	39.2	41.7	44.7††	43.0	46.3††	44.4	40.0
%	4		45.9	45.4	44.3	42.8	42.5		45.7	44.3	47.5	43.4	40.2
	40		46.3	45.9	44.1	34.0	42.3		45.8	43.5	45.5	41.8	40.0
	100		46.7	45.5	38.2*	41.4	39.7		41.6**	40.0	41.1**	44.6	35.5
% Neut.	0	6.6	11.9†	24.2†	31.8††	42.0	32.2††	7.7	14.3	24.2††	26.4††	35.6	33.4††
	4		12.9	23.5	36.1	31.3	32.2		15.4	23.1	22.6	30.6	39.2
	40		16.1	27.6	33.0	41.6	39.8		13.9	23.7	29.9	32.0	39.5
	100		20.9*	31.5*	48.3**	42.6	49.5**		25.3	34.8**	44.1**	50.4	54.4**
Platelets	0	92.4	678	711	614††	767	975	964	683	650††	528††	564	706†
X 1000	4		700	733	643	811	837		659	637	540	617	675
	40		689	678	637	1147	902		633	717	600	732	732
	100		631	733	923**	875	871		729	868**	723**	660	998*

* $P \leq 0.05$ when compared to controls
** $P \leq 0.01$ when compared to controls
† $P = 0.05$ for trend
†† $P = 0.01$ for trend

b. Clinical Chemistry

X	Electrolytes:	X	Other:
x	Calcium*		Albumin*
x	Chloride*		Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorous(Pi)*	X	Cholesterol*
x	Potassium*		Globulins
x	Sodium*	X	Glucose*
	Enzymes	X	Total Bilirubin*
X	Alkaline phosphatase	X	Total Serum Protein(TP)*
X	Cholinesterase(ChE)#!		Triglycerides
X	Creatinine phosphokinase(CPK)*°		Serum protein electrophoresis
X	Lactic acid dehydrogenase(LDH)	X	A/G ratio
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
X	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies
\# Should be required for OP
° Not required for subchronic studies
! Brain, RBC and Serum

NOTE: Although brain cholinesterase is a tissue measurement rather than a blood value, the results will be reported in this section of the DER.

Results - As can be seen in table 5, P_i was significantly increased about 10 to 12 % at 26 and 52 weeks in the high dose males and at 26, 52, 78 and 98 weeks in the mid (4 to 25 %) and high (10 to 33%) dose females. Calcium, although statistically significant (not on table) when compared to control values, was decresed less than 6 % in the high dose males (week 78) and females (weeks 52 and 78). There was also a statistically significant decrease (30 and 20%) in SGOT (table 5) for the high dose males (at 26 and 52 weeks, respectively), and a 50 and 70% increase in SGOT for high dose females at 52 and 104 weeks, respectively. LDH and CPK were statistically decreased (not on table) in the male and female high dose groups only at 26 and 52 weeks in males and at 52 weeks in females. TP (not on the table) was also slightly, but statistically, decreased ($\leq$ 11%) in mid (26 and 52 weeks) and high (26, 52, 78 and 104 weeks) dose females.

Cholinesterase - Brain cholinesterase (Brain ChE) in the mid and high dose rats was consistently depressed from 42 to 75 % of control values (see table 5). At 52 weeks, brain ChE was slightly, but statistically significant, depressed (14 %) in the low dose females. Although serum ChE was depressed in the mid and high dose rats throughout the study (2 to 66 % of control values), the values were statistically significant only after 1 year. RBC ChE depression ranged from 14 to 38% of control values in the mid and high dose rats Throughout most of the study.

Table 5 Select chemistry parameters

		Males						Females					
	Week	0	26	52	78	98	104	0	26	52	78	98	104
Test	PPM	N 10	10	20	10	5	10	10	10	20	10	5	10
SGOT	0	116	105††	116††	81	57	80	147	86	96††	94	98	59†
(U/L)	4		93	105	91	65	66		95	90	94	72	88
	40		91	105	80	52	68		111	114	84	57	76
	100		74**	93**	94	74	80		86	146**	102	116	101*
P_i	0	9.02	5.83†	5.04††	5.73	6.68	5.15	9.24	4.63††	3.88††	4.79†	4.96†	4.59
(MG/DL)	4		5.69	5.07	5.36	5.98	5.17		4.33	4.14	4.64	5.16	4.32
	40		5.85	5.03	5.18	6.88	5.60		5.48**	4.84**	4.99	5.36	5.06
	100		6.45*	5.66**	6.26	6.22	5.73		5.76**	4.89**	5.26*	6.58*	5.36
ChE	0	--	2490††	2442††	2060††	1296	1985††	--	1720††	2425††	2280††	1348	1875†
RBC	4		2670	2435	2170	1300	1900		1840	2379	2470	1434	1905
(MU/ML)	40		2280	2090**	1933	1374	1550**		1090**	2365	1940**	1204	1545*
	100		2130**	1860**	1670**	1116	1525**		1070**	2050**	1760**	1322	1513*
ChE	0	--	544†	763††	928††	1170	925	--	2239††	2451††	2095††	1999	1905††
Serum	4		417	802	862	757	741		2645	2642	2266	2197	1887
(MU/ML)	40		322*	562*	712	654	814		1820	1906**	1601	1531	1429
	100		381*	552**	405**	401	666		1351**	1581**	1266**	1962	1023**
ChE	0	--	--	3018††	--	2712††	2597††	--	--	3423††	--	2992††	2718††
Brain	4		--	3414*	--	2634	2389		--	2936**	--	2825	2595
(MU/ML)	40		--	1759**	--	1513**	1284**		--	1148**	--	1618**	1294**
	100		--	1347**	--	1472**	886**		--	1064**	--	1180**	717**

* $P \leq 0.05$ when compared to controls
** $P \leq 0.01$ when compared to controls
† $P = 0.05$ for trend
†† $P = 0.01$ for trend

6. Urinalysis°

Urine was collected from fasted rats at 26, 52, 78, 93 and 104 weeks. The CHECKED (X) parameters were examined.

X		X	
	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity(SpGr)*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

* Required for chronic studies
° Not required for subchronic studies

Urine volume (see table 6) was reduced 45 % at week 26 in high dose females. At 52 weeks the volume was reduced 56 and 68 % in mid and high dose females, respectively, and 17 % in the high dose males, when compared to controls. Although not statistically decreased, volume in the high dose females, remained about 22 % less than controls through the end of the study. Female groups with reduced volume also had a corresponding increase in urine SpGr at 26 weeks and 1 year. There were no treatment related changes in the other urinary parameters.

Table 6 Water consumption, Urine volume and specific gravity

		Males						Females					
	Week	0	26	52	78	98	104	0	26	52	78	98	104
Test	PPM	N 10	10	20	10	5	10	10	10	20	10	5	10
Urine Volume (ml)	0	- not done	22.00	21.72†	28.60	29.40	24.70	- not done	18.10††	26.00††	22.10	31.80	21.40
	4		23.20	21.45	20.10	38.80	33.30		23.30	27.05	33.99	34.80	26.90
	40		23.70	20.80	20.90	18.80	25.11		17.20	11.50**	30.40	31.80	21.30
	100		22.80	17.95*	20.60	20.20	25.56		10.00**	8.30**	17.67	24.40	16.70
Urine SpGr	0	1.036	1.046	1.046	1.038	1.034	1.035	1.037	1.031††	1.023††	1.029	1.026	1.029
	4		1.043	1.039	1.046	1.029	1.028		1.024	1.022	1.021	1.023	1.023
	40		1.039	1.040	1.043	1.047	1.031		1.033	1.029*	1.029	1.030	1.024
	100		1.042	1.043	1.043	1.036	1.032		1.042**	1.036**	1.036	1.030	1.031
Water consumpt. (gm/day)	0	- not done	37.81[1]	36.65[2]	46.65[3]	55.68[4]	57.80[5]	- not done	36.48†[1]	47.11††[2]	47.18[3]	59.88[4]	51.02[5]
	4		34.81	34.75	45.69	44.70	55.48		45.09*	56.24	56.66	51.35	54.30
	40		35.51	40.50	37.19	53.01	48.49		29.66*	47.18	48.80	50.14	49.22
	100		32.82	36.69	44.47	64.25	51.10		30.09*	35.89**	37.37	54.65	51.12

* $P \leq 0.05$ when compared to controls
** $P \leq 0.01$ when compared to controls
† $P = 0.05$ for trend
†† $P = 0.01$ for trend
[1] for weeks 24 through 28
[2] for weeks 52 through 56
[3] for weeks 76 through 80
[4] for weeks 92 through 96
[5] for weeks 100 through 104

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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.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
X	Tongue	X	Aorta*	XX	Brain*†
X	Salivary glands*	XX	Heart*	X	Periph.(sciatic)n.*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*[1]
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*	X	Eyes (optic n.)*
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*††
	Gall bladder*	X	Prostate		Other
X	Pancreas*	X	Seminal vesicle		Bone*#
	Respiratory	XX	Ovaries*†	X	Skeletal muscle*
X	Trachea*	X	Uterus*	X	Skin*#
X	Lung*		horns, cervix	X	All gross lesions
X	Nose°	X	Vagina		and masses*
	Pharynx°				
X	Larynx/pharynx°				

* Required for subchronic and chronic studies
° Required for chronic inhalation
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies
[1] only examined 2 levels

a. Organ weight

There were no treatment related changes in organ weights. Although the absolute liver weights were decreased in the high dose females at both 1 and 2 years, the corresponding relative (% of body weight) liver weights were not increased (see table 7).

b. Gross pathology

Although there was a table correlating masses observed at necropsy with microscopic observations, there was no summary of other post mortem observations. The text, however, does mention an increase in ulceration and/or inflammation of the skin in the high dose males and females.

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Table 7 Absolute and relative (% of body weight) liver weights

		Males			Females		
Sacrifice day		364	664	728	364	664	728
Test	PPM N=	9-10	5	19-26	9-10	5[1]	26-31
Absolute (gms)	0	21.99	16.87	19.57	14.47	11.97	16.82
	4	23.03	20.66	21.64	12.46*	11.29	15.95
	40	20.57	16.56	21.63	13.65	12.16	15.96
	100	17.74	15.67	18.36	9.93**	8.58	13.82**
Relative %	0	3.268	2.132	2.592	3.502	2.384	3.371
	4	3.275	2.777	3.023	3.347	2.355	3.194
	40	2.948	2.263	2.681	3.027*	2.050	2.806*
	100	2.715**	2.124	2.651	3.271	2.528	3.284

* $P \leq 0.05$ when compared to controls
** $P \leq 0.01$ when compared to controls
[1] N = 2 in the high dose group

c. Microscopic pathology

1) Non-neoplastic - There was a slight but statistically significant increase in hepatic telangectasia and pancreatic focal atrophy of acinar tissue noted only in the mid dose males. As can be seen in table 8, there was an increase in accumulations of foamy macrophages in the lungs in the high dose males and females. Skin lesions included increased ulceration and purulent inflamation also in the high dose males and females. The histologic lesions were not observed until the second year of the study.

2) Neoplastic - There were no treatment related increases in neoplastic lesions.

Table 8 Select non-neoplastic microscopic lesions[1]

organ lesion	dose (ppm)	males 0	4	40	100	females 0	4	40	100
	no. examined	80	80	80	79	80	80	80	80
Skin - ulcer		3	1	7	14**	1	1	2	3
- purulent inflam.									
acute		2	5	7	3	1	1	5	7*
chronic		3	0	6	11*	1	1	1	2
Lungs - accumulations of foamy macs.		10	6	13	23**	13	8	7	27**

[1] all animals regardless of time or manner of death
* $P \leq 0.05$ when compared to controls (Fisher's exact test)
** $P \leq 0.01$ when compared to controls (Fisher's exact test)

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D. DISCUSSION:

Treatment related clinical signs occurred in mid and high dose rats. These included alopecia, chromorhinorrhea and several neurologic signs (hypersensitivity to touch, fasiculation (females only), and tremors. Most of these, except for alopecia, appeared to decrease in intensity after the first year. The NOEL and LEL for these lesions were 4 and 40 ppm, respectively.

Body weight reductions in the high dose males and females were probably treatment related. Reductions in the mid dose males and mid and low dose females, however were probably not treatment related since they were sporadic and less than 10 % of control values. As a result, the body weight NOEL and LEL for both sexes is 40 ppm and 100 ppm, respectively.

Food consumption was slightly and minimally increased in the high dose males and females, respectively. The changes in the mid dose group were probably not toxicologically relevant due to their sporadic nature. The consumption changes, when combined with body weight data, suggest a decrease in food efficiency primarily in the high dose. It is possible that the slight increase in food consumption in the high dose males, minimized their weight gain depression (less than 13 %) while the high dose females, with only a minimal increase in food consumption, tended to weigh 20 % less than controls. The NOEL and LEL for both sexes for food consumption is 40 ppm and 100 ppm, respectively.

The ocular changes observed by the ophthamologist appeared to be incidental or related to the periorbital bleeding procedure rather than to treatment.

Treatment with methidathion in the diet was probably responsible for the slight increase in platelets and absolute neutrophilia in the high dose males and females as well as the associated reversal of the neutrophil:lymphocyte ratio. Changes in the other hematologic parameters were probably not treatment related since the values occurred sporatically and were usually within the expected range for the rat. The increased serum P_i observed in the high dose males and mid and high dose females may be related to organophosphate ingestion. Although hypocalcemia may also be associated with phosphate ingestion, the slight decreases (6% and less) observed in the high dose males and females were sporadic and within the normal range. Although the increased SGOT in the high dose females, may have been related to treatment, it occurred at only two time points and the values were within the normal range. Decreases in SGOT, LDH, and CPK are not usually clinically significant and the values were within normal ranges. The TP values (less than controls) in the mid and high dose, were also within the normal range and probably not treatment related.

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Chronic ingestion of methidathion at 40 ppm and above, resulted in RBC, serum and brain ChE inhibition throughout the study. Although brain ChE was decreased in the low dose females at all time points, it was probably not treatment related since the decrease was statistical only at one year, was not associated with a decrease in the other ChE parameters. The NOEL and LEL for ChE (all three) were 4 and 40 ppm, respectively. The NOEL of 4 ppm for brain ChE inhibition is consistent with results seen in a 22 week rat feeding study.

The authors concluded that the decrease in urinary volume and corresponding increase in SpGr noted in the female rats was related to decreased water consumption. This is a reasonable assumption since there were no microscopic and clinical chemistry alterations suggestive of renal toxicity. Although urinary volume was decreased in the high dose males, it was not as consistent or as marked as in the females, and there was no the corresponding SpGr increase or water consumption decrease.

There were no treatment related changes in organ weights. There were no summary tables of gross observations noted at necropsy. This data was only available from the individual animal pathology records. There was, however a summary correlating all masses noted at sacrifice, with a microscopic diagnosis. Treatment related non-neoplastic pathology was limited to inflammatory and ulcerated lesions of the skin and accumulations of foamy macrophages in the lungs in the high dose of both sexes. The company stated that the lung lesions were probably not treatment related since they were small, however they did not submit any data to support this claim. Hepatic telangectasia and pancreatic lesions did not appear to be treatment related since the increases were limited to the mid dose males. The NOEL and LEL for non-neoplastic pathology was 40 and 100 ppm, respectively. The tumor data did not indicate any treatment related increases in neoplastic lesions after statistical analysis, both with and without survival corrections.

Appendix I

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APPENDIX II-1

Statistical Methods

Body Weight, Food Consumption, Organ Weight: All numerical data that were obtained during the course of the study were submitted to Management Services, Ardsley, for storage in the NO5 system of the IBM 3034 computer and interim or final reports were generated using a program developed by the Research Statistics Section of CIBA-GEIGY. This program routinely lists individual animal data and provides summary tables and performs the following statistical analyses: a test for outliers (1) and Bartlett's test for homogeneity of variance (2); if the Bartlett's test was not significant at $p \leq 0.05$, then a statistical comparison of treated group means to control group means was performed using Dunnett's t test (3); if Bartlett's test for homogeneity of variance was significant, then Behren's t test with Cochran's approximation (4) was employed. Appropriate transformations (e.g., logarithmic, or square root) were applied to a predetermined set of parameters which were not normally distributed. Certain spare organ weight parameters were analyzed by using the Statistical Analysis System (5,6) with the same statistical methods.

Clinical Laboratory and Water Consumption Data: All numerical data that were obtained in the course of study were submitted to Research Computing Services or Scientific Systems for storage and for generation of interim/or final reports on programs developed by the Research Statistics Section of CIBA-GEIGY. These programs routinely list individual animal data and provide summary tables, and when the design requirements are met, generate statistical analyses. These analyses are designed mainly to test each parameter for possible trends existing between treatment groups that comprise different doses of the same compound and a zero dose control. If a significant trend is found, the test procedure is applied again to the remaining treatment groups, excluding the highest dose group, and so on, in order to examine the significance of comparisons of dose groups against the control.

Mortality Data: The number of days on test were regarded as the true death dates for animals that died or were sacrificed moribund and as censored times for animals sacrificed on a schedule. Individual mortality data were analyzed by the Research Statistics Section of Ciba-Geigy using the Statistical Analysis System (5,6). The survival distribution for each group and each sex were determined using Kaplan-Meier estimates (15) and were plotted. Estimates of the percentiles of the distributions were also provided. Nonparametric rank tests (7,8) (Generalized Wilcoxon test and Mantel-Cox logrank test) were performed separately for each sex to test for differences between the survival curves of the treatment groups. If significant differences were found, multiple comparisons were then performed to compare each treated group versus the control.

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METHIDATHION: 2-YEAR ORAL ONCOGENICITY AND TOXICITY STUDY IN ALBINO RATS (MIN 832001)

Pathology Data: All data from individual animals including tumor data were entered by the pathologist into the NO3 Pathology Data Base in the IBM computer. The microscopic data were tabulated and incidence tables were generated by the NO3 pathology data system. If samples sizes were adequate, these data were analyzed separately for each sex by Fisher's exact test (9) and for both sexes by computing the convolved probabilities (10).

Pathology Tumor Data: The general method of Peto (11), later justified in theory by Lagakos (12) was used to evaluate possible treatment-related effects on tumor incidence. Cause of death information were utilized to classify tumors as either incidental (tumors which did not cause death) or fatal, and the statistical analysis was adjusted for differential mortality rates between groups. Mantel's time-adjusted trend test (16) or Tukey's exact version of this test (13) was used to evaluate the observed and expected incidences of tumors which were considered to have caused the animal's death. The logistic regression method of Dinse and Lagakos (14) were used to evaluate the observed and expected incidence of tumors that were considered mortality independent. If the overall trend test obtained by combining the results from the two separate analyses was significant, subsequent multiple comparisons of lower dose groups versus the control group were performed by repeating the entire analysis after excluding the data from the highest dose group, this process was repeated until either a non-significant result was obtained or all treated groups had been compared to the control group. For palpable tumors, the same test procedure used for fatal tumors (16,13) was employed, where the time to response was the 'onset time' (i.e., the earliest time that the tumor was palpated) of each tumor (see Appendix II-2 for more details).

Cliff Meng 4/7/86

Cliff Meng, Ph.D. Date
Safety Statistics Group Leader

Lilly Sanathanan 4/8/86

Lilly Sanathanan, Ph.D. Date
Associate Director, Research Statistics

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June 11, 1986

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2 262324
3 262324
4 262325
5 262326

Mr. Larry Schnaubelt
Product Manager (12)
Registration Division (TS-767C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall 2 - Room 202
Arlington, VA 22202

Dear Mr. Schnaubelt:

SUBJECT: METHIDATHION REREGISTRATION
SUBMISSION OF FINAL REPORT OF TWO-YEAR ORAL ONCOGENICITY AND TOXICITY STUDY IN ALBINO RATS
CIBA-GEIGY TECHNICAL METHIDATHION
EPA REG. NO. 100-530

Enclosed are two copies of the final report of the following study:

Methidathion: Two-Year Oral Oncogenicity and Toxicity Study in Albino Rats. Toxicology/Pathology Report 86061 (MIN 832001). Research Department, Pharmaceutical Division, CIBA-GEIGY Corporation. May 23, 1986.

Each copy of the report consists of five volumes, totalling 1,994 pages. Please forward the five accession numbers assigned. Please use the enclosed extra copy of this letter on which to record the accession numbers and return it to us. CIBA-GEIGY considers the contents of these volumes to be CIBA-GEIGY proprietary information. Although these data are subject to release to non-multinationals under Section 10 of FIFRA, they are considered trade secret by CIBA-GEIGY for all other purposes.

This study fills the requirement for one of the two species required for oncogenicity testing, as listed in the guidance document for reregistration of methidathion. The oncogenicity study for the other species (mouse) was submitted March 26, 1986. The remaining studies to complete the toxicology requirements (rat reproduction, 21-day dermal, and rabbit teratology) for technical methidathion will be submitted prior to the January 18, 1987 deadline.

To summarize the enclosed two-year rat study, methidathion technical was administered in the diet to 65 male and 65 female albino Sprague-Dawley rats for 104 weeks at concentrations of 0, 4, 40 and 100 ppm. Fifteen additional rats/sex/group were assigned to each group; ten of these were sacrificed after 52 weeks on test and 5 rats/sex/group were killed at week 93.

Study results show that methidathion technical is not oncogenic in the rat when administered in the diet at feeding levels of up to 100 ppm. Significant

reductions in body weight and water consumption and increased feed consumption as well as clinical signs indicative of cholinesterase inhibition were observed at feeding levels of greater than or equal to 40 ppm.

Clinical laboratory studies demonstrated consistent dose-related reductions in serum, RBC, and brain cholinesterase levels and increased inorganic phosphorus levels at feeding levels of 40 ppm and greater. Other differences that were observed between the treated and the control groups in hematological, clinical chemistry, and urinary parameters were generally small in magnitude and did not correlate with any gross or microscopic evidence of specific organ pathology.

The only microscopic finding that appeared related to treatment was an increased incidence of skin lesions and of focal accumulations of foamy macrophages in the lungs of high-dose animals. These changes are likely to be indirect effects of compound administration and are considered to be of no toxicological significance. Other gross and microscopic findings observed include neoplastic changes that are commonly seen in a population of aging rats and are not considered to be related to treatment with methidathion technical.

Based on these results, it is concluded that methidathion technical is not oncogenic in the rat. The maximum tolerated dose was established at 100 ppm and the no-effect level was 4 ppm.

Sincerely,

Richard L. Conn

Richard L. Conn
Senior Regulatory Specialist

RLC/ms/0203

Enclosures

and its metabolites, sulfoxide and sulfone, are not expected to exceed 0.06 ppm in meat, 0.025 ppm in milk, 0.10 ppm in poultry tissues and 0.05 ppm in eggs. Residues not exceeding these levels may enter interstate commerce. The Food and Drug Administration, DHHS, has been advised of these conclusions. The Agency will expeditiously move towards establishing Section 409 tolerances for citrus oil and refined cottonseed oil and Section 408 tolerances for meat, milk, poultry and eggs. Data on residues of cottonseed soapstock must be submitted in order to determine whether a food additive tolerance is needed for soapstock. The tolerances for residues of methidathion on almonds, walnuts and pecans established under Section 408 of FFDCA will be revoked by the Agency because they have been superseded by the existing group tolerance for nuts which was established on October 2, 1978.

D. Regulatory Rationale

The Agency has reviewed the available data concerning toxicology, environmental fate, residue and product chemistry, and ecological effects. Sufficient data are available to show that technical methidathion has a high acute oral and dermal toxicity to mammals and is assigned to Toxicity Categories I and II, respectively. Acute intoxication signs characteristic of acetylcholinesterase poisoning were demonstrated by the data. No data were available to assess the acute inhalation toxicity of technical methidathion or the acute effects for the formulation intermediate products. Data on the technical product demonstrate a potential for slight eye and dermal irritation. However, testing on the manufacturing-use products is required to fulfill Agency data requirements. Data also demonstrate that methidathion is not an acute delayed neurotoxin.

The histopathology data in an oncogenicity study in mice (Barnett et al., 1980) indicated statistically significant increases in the frequency of hepatocellular carcinomas and hepatocellular adenomas in male mice at the high dose level (100 ppm). However, this study, conducted by Industrial Bio-Test Laboratories, is deficient in several important respects (related to the way in which the study was conducted) and has been determined to be invalid in a review carried out by Health Protection Branch, Health Canada. New oncogenicity studies, using the mouse and an additional species, preferably the rat, are required.*/

*/ These studies are being voluntarily initiated by Ciba-Geigy due to the fact that Canada found the IBT mouse oncogenicity study to be invalid. The mouse study was begun in November, 1982, and the rat study will start in the first quarter of 1983. Interim reports will be available in early 1984 and final reports in 1986.

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Ordinarily, a finding of potential oncogenicity in chronic effects testing could lead to the initiation of a "Rebuttable Presumption Against Registration" (RPAR) in order to weigh the risk of continued use against the benefits of that use. However, Section 3(c)(8) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) directs the Agency not to initiate a Rebuttable Presumption Against Registration action, unless a validated test or other significant evidence indicates prudent concerns of unreasonable adverse risk to man or the environment. Because the mouse oncogenicity study was found invalid in the IBT review by Canada, the most appropriate regulatory action is to move expeditiously in filling the data gaps.

Section 409 of the Federal Food, Drug, and Cosmetic Act (FFDCA) requires that tolerances be established for any pesticide residues concentrating in processed foods/feeds. A review of the residue data showed that there are finite residues of methidathion in citrus oils and refined cottonseed oil. While tolerances have been established under Section 408 of the FFDCA for methidathion residues in or on citrus and cottonseed as raw agricultural commodities (RAC), no Section 409 food additive tolerances exist for citrus oil or refined cottonseed oil. Citrus oil or refined cottonseed oil containing any residues exceeding the RAC tolerances could be seized as "adulterated food" by the Food and Drug Administration in the absence of such tolerances.

At the time the tolerance was established for cottonseed, a 409 tolerance was not needed because methidathion was approved for use on cotton before the bolls were open and the residue data indicated that the residues in the oil were lower than the residues in the cottonseed. Later, however, the use of methidathion on open cotton bolls was granted resulting in greater linter and seed exposure and oil residues which are higher than the cottonseed residues. The Agency should have required a 409 tolerance for that use but apparently overlooked it through administrative error. Based on available data, a food additive tolerance of 0.5 ppm should be established for cottonseed oil. Data on residue levels in soapstock are needed to determine whether a food additive tolerance is needed.

When RAC tolerances were established for citrus, a food additive tolerance was not set for citrus oils because it was thought that these oils were used at such low concentrations as flavoring agents that any residues in the final flavored food would be below the tolerance for citrus and probably at non-detectable levels. However, in 1978 this policy was questioned in connection with the chlorobenzilate RPAR. The Agency changed the policy in 1978 for several reasons: (1) citrus oils shipped interstate could be seized by FDA if residues exceed the RAC tolerance for citrus; (2) food additive tolerances had been previously set for mint oil, which is used at low concentrations as a flavoring agent; and

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(3) a number of food additive tolerances had been established for various spices, which are also used at low levels as flavoring agents. Now the policy is to require data for cold pressed citrus oils and to establish a food additive tolerance when residues on the oils exceed the RAC tolerance for citrus. Because residues of methidathion in citrus oils (400 ppm) exceed the RAC tolerance (2 ppm), a food additive tolerance is needed.

In addition to these food additive tolerances, tolerances for meat, milk, poultry tissues and eggs need to be established. A review of existing data indicates that residues of methidathion and its metabolites, sulfoxide and sulfone, are not likely to exceed 0.06 ppm in meat, 0.025 ppm in milk, 0.10 ppm in poultry tissues and 0.05 ppm in eggs.

To bring the tolerances in line with current policies and to avoid the potential for seizure by FDA of legally treated commodities, the Agency will move expeditiously to establish food additive tolerances for citrus oils and cottonseed oil and to establish tolerances for meat, milk, poultry tissues and eggs.

Since the Agency is concerned about the indication of oncogenicity in the IBT mouse study, we intend to set an expiration date for the above tolerances of five years. This time period will allow the oncogenicity studies to be submitted and reviewed by the Agency in conjunction with the entire toxicological data base to determine if the food additive tolerances should be continued. In the interim, the Agency is establishing maximum residue limits for citrus oils, cottonseed oils and meat, milk, poultry tissues and eggs as specified above. The Agency is notifying the FDA that commodities containing these residue levels are acceptable and should not be seized. In addition, the Agency will evaluate any petitions for new or increased tolerances carefully to assure that the incremental residue contribution is insignificant.

The available methidathion environmental fate data are insufficient to fully assess this chemical at this time. However, from the available information, methidathion does not appear to represent an environmental hazard based on its current use pattern. It degrades fairly rapidly in the soil with a half-life of about 14 days and has a low bioaccumulation potential. Photodegradation should be a minor degradation pathway under natural conditions. Unaged residues are slightly mobile in medium to fine textured soils and immobile in organic soils. Both aged and unaged residues are mobile in coarse textured soils. The rapid degradation of methidathion in soil appears to mediate its potential to contaminate ground water in coarse textured soils.

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Chemical:	**Methidathion**
PC Code:	**100301**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/26/87 12:00:00 AM**
File ID:	**TX0005743**
Accession Number:	**412-04-0141**

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