(6-12-86) G. Ghali

007590

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Guthion (Azinphosmethyl) CAS #: 86-50-0
Caswell #: 374

Carcinogenicity: Equivocal evidence of pancreatic islet cell and adrenal cortical neoplasms in the rat. Judged to be a Category "D" tumorigen in the abbreviated Peer Review of 5/28/86. Negative tumorigenic effect in two mice studies.

Systemic Toxicity: See below.

Preparation Date: 6/12/86

Endpoint	Experimental Doses	UF	MF	RfD
Mobay and Bayer (1966)	5 ppm (0.125 mg/kg/day) ~~ChE~~ NOEL RBC	10	10	0.0013 mg/kg/day
2-Year Dog Feeding Study	39.2 ppm (1.96 mg/kg/day) (TWA) ChE LEL			
dose-dependent decrease in cholinesterase (blood)				
reduced feed and body weights; fine tremors of limbs	135.7 ppm (TWA) Systemic effects			

Conversion factor (dog): 1 ppm = 0.025 mg/kg/day

Endpoint and Experimental Doses:

Noel, P.R.B., et al. (1966)
Gusathion (Bayer 17147) Chronic Oral Toxicity Study in Dogs
Huntingdon Research 1656/66/184; Study No. 19798. Final report received April 7, 1970; submitted by Mobay Chemical Corp.

Four groups of 4 pedigree Cocker Spaniel dogs per sex were offered diets containing Azinphosmethyl as folows: 0 ppm (control) and 5 ppm (low dose) for 105 weeks (TWA = 5 ppm); 20 ppm for 36 weeks then 50 ppm for 69 weeks (mid-dose; TWA = 39.7 ppm); and 50 ppm for 36 weeks, 100 ppm for 21 weeks, 150 ppm for 27 weeks and 300 ppm for the final 21 weeks (high-dose; TWA = 135.7 ppm). Animals were subjected to standard toxicological evaluation under satisfactory GLP conditions during compound ingestion. Clinical signs included fine muscle tremors of the hind limbs, drooping of the head

Endpoint and Experimental Doses (cont):

and staggering. These signs appeared in the high-dose animals only. Body weight and food consumption were similar for the control and low and middle dose animals but these measurements were reduced in the high-dose animals after the dosage was increased to 300 ppm at week 85. RBC ChE inhibition was noted in the mid- and high-dose animals. No other adverse effects were reported for any clinical or histopathological parameters. No tumors were reported in any animal.

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Uncertainty Factors (UFs):

An uncertainty factor of 10 was used to account for the inter- and intraspecies differences in the extrapolation of ChE inhibition form dog to man.

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Modifying Factors (MFs):

A modifying factor of 10 was used to account for the lack of adequate chronic data (a new rat study) and the lack of adequate teratology-reproduction data.

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Additional Comments:

The Toxicological Branch Abbreviated Review Committee meeting on 5/28/96 classified Azinphosmethyl as a Category D oncogen, equivocal of tumorgenicity based on an NCI study in rats.

Data Considered for Establishing the RfD

1) 2-Year Feeding - Dog ChE NOEL = 5 ppm (0.125 mg/kg/day), ChE LEL = 39.2 ppm (1.96 (1.96 mg/kg/day)(TWA)(dose-dependent decrease in cholinesterase (blood)); Systemic effects at 135.7 ppm (TWA); reduced feed and body weights; fine tremors of limbs; core grade minimium

2) 2-Year Feeding/Oncogenic - Rat ChE NOEL = 5 ppm (0.25 mg/kg/day), ChE LEL = 20 ppm (1.0 mg/kg/day)(slight blood cholinesterase inhibition; 50/100 decrease brain and blood cholinesterase); Oncogenic NOEL > 50/100 ppm; no core grade

3) 3-Generation Reproduction - Mice Reproductive NOEL = 25 ppm (3.75 mg/kg/day), Reproductive LEL = 50 ppm (7.50 mg/kg/day)(HDT; reduced lactation index); no core grade

4) Teratology - Rat Terata NOEL $\geq$ 5.0 mg/kg/day (HDT); Maternal toxicity = 5 mg/kg (Decreased weight, reduced pup weight and decreased weanling survival); no core grade

5) Teratology - Rabbit Teratogenic NOEL > 3 mg/kg/day (HDT); Maternal NOEL > 3 mg/kg/day (HDT); Fetotoxic NOEL > 3 mg/kg/day (HDT); core grade supplementary

Data Gap(s)

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1) Rat Reproduction Study

Other Data Considered

1) 2-Year Oncogenic - Mice Oncogenic NOEL = 100 ppm (15 mg/kg/day), Oncogenic LEL = 400 ppm (60 mg/kg/day)(hepatocellular tumors, females); Systemic NOEL < 25 ppm (3.75 mg/kg/day)(female - liver hyperplastic nodules, telangiectatic and basophilic focus; male - spleen hematopoiesis; Male and Female - stomach hyperkeratosis); core grade minimum

2) 1-Month Feeding - Human ChE NOEL = 1.5 mg/kg (highest level tested; plasma erythrocyte ChE); no core grade

3) 4-Weeks Feeding - Human ChE NOEL > 6.0 mg/day (plasma or erythrocyte ChE); no core grade

4) Teratology - Rabbit Terata NOEL = 25 ppm; no core grade

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Confidence in the RfD:

Study: High Data Base: Medium RfD: Medium-~~High~~

The critical study is considered to be of ~~excellent~~ quality and is given a ~~high~~ confidence rating. The supporting data base is of good quality but is deficient in several critical areas such as reproduction/teratology and a chronic rat study. The RfD is given a medium ~~to high~~ confidence rating.

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Documentation of RfD and Review:

Registration Files

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Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary: ~~David L. Ritter FTS 557-7375~~

Secondary: ~~R. Bruce Jaegar FTS 557-0699~~

4/10/82

GUR 6010

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CHRONIC TESTING

83-1 Chronic Toxicity - Rodent and Non-rodent

Study Type: Chronic Oral (feeding) in Dogs with Gusathion

Accession Number: 091498

MRID Number: 00083620

Sponsor: Farbenfabriken Bayer AG; #19798

Contracting Lab: Huntingdon Research Centre, England

Date: July 13, 1966

Test Material: Gusathion, under the code of "BAY 17' 147";
Common name: Azinphos-methyl.

Test Animals:

Male and female pedigree Cocker Spaniel dogs of no specified age were housed individually in kennels with water ad libitum and acclimated to the laboratory for 2 months before the start of the study. Each dog was fed 400 g of dry diet daily: half in the morning and half in the afternoon.

Procedure:

Dogs were marked with a number and assigned to four groups of 4/sex each of which were fed dietary levels of Gusathion as follows:

0 ppm for 105 weeks (control)

5 ppm for 105 weeks (low dose)

20 ppm for 36 weeks, then 50 ppm for 69 weeks (intermediate dose)

50 ppm for 36 weeks, 100 ppm for 21 weeks, 150 ppm for 27 weeks, and 300 ppm for the last 21 weeks (high dose)

High and intermediate dose levels were increased at the above intervals due to the absence of toxic symptoms. Gusathion was mixed with a finely powdered dry diet at the indicated concentrations by Farbenfabriken Bayer AG before shipment to Huntingdon Research Centre. All dogs received the same quantity of food as before. Each dog also received 1/3 pint of milk at noon during the first 6 months of the dosing period. All dogs were observed 3 or 4 times daily and weighed once weekly.

Individual plasma and erythrocyte cholinesterase levels were determined weekly during the 5 weeks immediately prior to dosing and every 4 weeks thereafter. Routine nematology examinations, clinical chemistry determinations and urinalyses were conducted for all dogs prior to dosing and after 6, 12, 24, 36, 52, 64, 76, 88 and 100 weeks of dosing.

All surviving dogs were sacrificed under anesthesia after 2 years exposure to Gusathion. All dogs that died during the study and all sacrificed dogs underwent complete post-mortem examinations. The following organs were weighed: brain, pituitary, heart, lungs, liver, spleen, pancreas, thyroids, thymus, adrenals, kidneys, gonads and uterus/prostate.

Specimens from the following tissues and organs were reported taken from all dogs and fixed in buffered formalin for subsequent histopathological examination:

- Aorta-arch
- Aorta-abdominal
- Trachea
- Heart
- Lungs
- Thymus
- Lymph nodes-cervical and mesenteric
- Liver
- Gall bladder
- Spleen
- Pancreas
- Kidney
- Bladder
- Prostate/Uterus
- Ovaries/Testes
- Thyroid
- Adrenals
- Salivary gland
- Esophagus
- Stomach
- Duodenum
- Jejunum
- Ileum
- Colon
- Skin
- Skeletal muscle (3 levels from hind limb)
- Brain
  - Cerebral cortex
  - Basal nuclei
  - Mid-brain
  - Medulla
  - Cerebellum
- Eye
- Optic nerve
- Pituitary
- Sciatic nerve (2 levels above and below stifle joint)
- Spinal cord (3 levels)

Results:

One high dose male dog died during the 94th week of dosing, the 10th week of ingesting 300 ppm Gusathion. The definitive cause of this death was cholangitis which was accompanied by generalized jaundice.

Clinical symptoms were observed only in dogs in the high dose group after the dietary concentrations of Gusathion was finally increased to 300 ppm at week 85 of dosing. Fine muscle tremors of the hind limbs of the dogs were frequently observed. These tremors appeared with no ordered regularity or predictability from weeks 85 through 104, usually during periods of inactivity or abnormal quietness. Drooping of the head and staggering gait were observed periodically also.

Mean body weight gains and mean food consumption were comparable throughout the majority of the dosing period. However, there was reduced food consumption and body weight loss in dogs in the high dose group after the dietary concentration of Gusathion was increased to 300 ppm at week 85 of dosing.

Erythrocyte cholinesterase (ChE) was significantly inhibited at doses of 20 ppm and higher. There was slight plasma ChE inhibition at the 50 ppm dietary level and significant plasma ChE inhibition at 150 and 300 ppm. Laboratory data (hematology, clinical chemistry, urinalysis) revealed no differeces between treated and control groups to suggest an effect of Gusathion on these dogs. Gross and microscopic examination of organs and tissues detected no consistent changes or abnormalities which were dose/compound related. Weights of selected organs were within normal limits in all dogs and no tumors were observed in any of these dogs.

Conclusion:

The study began with four groups of male and female dogs which were fed dietary dose levels of Gusathion at 0, 5, 20 and 50 ppm. After 36 weeks of dosing, the intermediate and high dose levels were increased to 50 and 100 ppm, respectively, due to the absence of toxic symptoms. The high dose level was further increased to 150 ppm after 57 weeks and finally to 300 ppm after 84 weeks of dosing. The ingestion of Gusathion by dogs at stated dose levels for 2 years produced no lesions or alterations in morphology which could be dose/compound related. Erythrocyte ChE inhibition was detected at 20 ppm or more while plasma ChE inhibition occurred at 50 ppm and higher. Clinical symptoms (muscle tremors, weakness, lethargy), reduced food consumption and body weight loss were observed in the high dose group after the final increase to 300 ppm.

RBC ChE NOEL = 5 ppm
Plasma ChE NOEL = 20 ppm
NOEL (other than ChE) = 150 ppm

Classification: Core-Minimum

TS-769:ROBINSON:sll:X73710:4/3/86 Card New

037590

UNITED STATES GOVERNMENT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE
Food and Drug Administration

Memorandum

TO : Mr. Drew Baker
Petitions Review Branch (BC-13)

DATE: November 20, 1969

FROM : Dr. [redacted]
Division of Pharmacology [redacted]
Petitions Review Branch (BC-170)

SUBJECT: Guthion (O,O-dimethyl S(4-oxo-1,2,3-benzotriazin-3(4H)-ylmethyl)-phorphorodithioate), tolerances requested at 0.3 ppm on beans (dry), blackeyed peas, filberts, pecans, potatoes, and walnuts; on soybeans at 0.2 ppm; in milk (negligible residue) at 0.01 ppm; and in soybean oil at 1 ppm.

PESTICIDE PETITION NO. [redacted]
FOOD ADDITIVE PETITION NO. [redacted]

[redacted]
Kansas City, Missouri 64120
(AE 70-47)

Toxicity data previously submitted on Guthion are sufficient to judge safety of usage of this compound (Cf. DFT memo by M. Quaife, dated March 24, 1967, in PP No. 7F0-539).

However, Petitioner has included some new studies in this petition. Pertinent ones (excluding any on dermal or inhalation toxicity) are reviewed below.

Pertinent new toxicity studies:

Rat, 2-year feeding-study:

Study carried out at the Institut fUr Toxikologie of Farbenfabriken Bayer AG., Wuppertal-Elberfeld, Germany. Rats were of Wistar strain.

Rats and Dosage-levels

Group #	ppm Guthion in diet	No. of rats (M)		No. of rats (F)	
		P	S	P	S
1	50-100*	30	10	30	10
2	20	30	10	30	10
3	5	30	10	30	10
4	Control	30	10	30	10
5**	2.5	30	10	30	10
6	Control	20	10	20	10

* Changed to 100 at week 47.
** Groups #5 and 6 added to study 5 months after first 4 groups were begun.
P denotes main group; S denotes subsidiary group used for lab. tests (urinalysis, blood cholinesterase, etc.) until enough rats had died for latter part of study to necessitate use of "P" animals.

PCG

HELP ELIMINATE WASTE HEW COST REDUCTION PROGRAM

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Duration. 2 years

Mortality. No significant differences from the controls.

Body Weight. No significant effect on growth, food consumption, or efficiency of food utilization.

Organ Weight. No effect on organ weights (adrenals, brain, heart, kidneys, liver, lungs, ovaries or testes, uterus or prostate, spleen, and thyroid).

Clinical Laboratory Tests. No effect on results of urinalysis at 2, 52, and 96 weeks (for pH, sp.gr., protein, reducing substances, glucose, ketones, bile pigments, bile salts, urobilinogen) or of microscopic examination at same intervals. No effect at 2, 52, and 96 weeks on hematological values (for packed cell volume, Hb, RBC, WBC and differential count, mean corpuscular Hb content, and mean cell volume) for rats in groups 1 and 4 and also at 96 weeks for rats in groups 5 and 6.

Cholinesterase (ChE) Values. Assays made on plasma and erythrocytes, as follows:

Method	Groups	Weeks
Michel*	1 - 4	2, 10, and 26
	5 - 6	2
Williams, Frawley, and Fuyat**	1 - 4	39, 52, 65, 91, and 97
	5 - 6	10, 26, 39, 52, 65, 78, 91, and 97

(At week 2, no assays made on rats of groups 2 and 3.)

At termination, brains were assayed by method of Frawley, Hogan, and Fitzhugh, J. Pharm. exp. Ther. 105, 156 (1952).

Results. No effect on plasma cholinesterase or on RBC-ChE in male or female rats at 2.5 or 5 ppm. Rats at 20 ppm had occasional plasma ChE values less than 80% of control values and RBC-ChE values as low as 60% of controls, with very wide fluctuations in RBC-ChE. Both plasma and RBC levels of ChE were significantly depressed--to as low as 40% of control levels--in male and female rats at the 50-to-100-ppm level. Brain ChE was significantly depressed only in the highest-level group and much more so in female than in male rats.

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* J. Lab. Clin. Med. 34, 1,564 (1949).
** J. Assoc. Off. Agric. Chem. 40, 1,113 (1957).

Neoplasms. No effect.

Miscellaneous. A few female rats had convulsions after the dose-level for rats in Group 1 was raised to 100 ppm.

Histopathology. No effect.

"No-Effect Level." 5 ppm, based on lack of ChE inhibition in plasma or RBC's. Overt "no-effect level" is 50 ppm.

Dog, 19-week study* of effect on cholinesterase:

No. of Animals. 1 M and 1F per group.

Feeding-Levels. 0, 20, 50, 100, 200, and 400 ppm.

Effect on ChE. All treated dogs showed ChE inhibition (whole blood) which reached a maximum at the 4th or 5th week; it varied from about 35% in 20-ppm dogs to about 80% in 400-ppm ones, the degree of inhibition being in proportion to dose. Dogs at most dose-levels generally showed less inhibition in succeeding weeks. By the end of the test-period, those at 20 ppm had less than 20% inhibition. However, in 6 of 20 test-intervals, inhibition for this group exceeded 20%; therefore, 20 ppm is an "effect-level."

A separate experiment seemed to show that time of day at which blood samples are taken (with respect to time at which animals receive the test compound in the diet) does not influence blood ChE results in chronic feeding tests.

Body Weight; Dogs at 20 ppm lost no weight. "Rates of 50 ppm and higher caused reductions in body weight." Only the F dog at 400 ppm lost weight.

Behavior. Dogs at 50 and 100 ppm "appeared weakened and ill." Those at 100 ppm had occasional muscle spasms and tremors. Those at 200 and 400 ppm had trembling and severe muscle spasms.

Mortality. The F dog at 400 ppm died after the 9th week in "cachetic condition."

No-Effect Level. None shown (but at least 20 ppm) with respect to ChE in blood; 20 ppm for overt effect.

* Carried out in Germany at Institut für Toxikologie of Farbenfabriken Bayer A-G.

Dog, 2-year feeding-study:

Study carried out at the Institut für Toxikologie of Farbenfabriken Bayer A-G., Wuppertal-Elberfeld, Germany. Dogs were "Pedigreed cocker spaniels."

No. of Animals. 4 M and 4 F per group.

Feeding-Levels. 0 ppm; 5 ppm; 20 ppm for 36 weeks then 50 ppm for 15 months; and 50 ppm for 36 weeks, 100 ppm for 21 weeks, 150 ppm for 27 weeks, and 300 ppm for 21 weeks.

Duration. 2 years.

Body Weight. Possible slight decrease in body weight in dogs after transfer to 300 ppm; otherwise, no effect.

Behavior. In dogs at 300 ppm, the following symptoms were frequently seen: "Tremor of body musculature, abnormal quietness, and muscular weakness of neck or of hind limbs." (All dogs had semi-solid or liquid stools--ascribed to the dry diet used.)

Mortality. A female dog died during the 94th week of obstructive jaundice due to cholangitis after it had been on 300 ppm for 9 weeks.

Cholinesterase (ChE) Levels.

Plasma: Dogs at 5 and 20 ppm--no effect; those at 50 ppm--slight (up to 25%) inhibition after about a year; dogs at 100 to 150 ppm--slight-to-moderate (up to 35%) inhibition; animals at 300 ppm--pronounced (ca. 50%) inhibition.

RBC : Dogs at 5 ppm--no effect; those at 20 ppm--moderate (up to 35%) inhibition; dogs at 50 ppm--pronounced (up to 55%) inhibition; those at 100 to 150 to 300 ppm--severe (up to 80%) inhibition. (Both plasma and RBC-ChE values were determined 5 times before dosage and monthly thereafter.)

Hematologic Values. No effect. (Examinations included: Platelet counts every 6 months. Erythrocyte sed. rate (ESR), packed cell volume (PCV), hematocrit, Hb, RBC, WBC and differential white cell count, reticulocyte count, prothrombin index, and MCHC* and MCV**-- each determined once before dosing commenced and after 6, 12, 24, 36, 52, 64, 76, 83, and 100 weeks after dosing began.)

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* MCHC = Hb (g-%) x 100 divided by PCV.

** MCV = PCV (%) x 10 divided by RBC (millions per cubic mm).

Biochemical Assays. (other than ChE) No effect, except in the one dog that died (Cf. under "mortality"); she had at various times elevated BSR, high bilirubin level, high serum alkaline phosphatase, and high S-GPT and S-GOT and isocitric dehydrogenase; these were due to obstructive jaundice with less marked hepatic parenchymal damage. (Examinations included: Blood urea, blood sugar, total serum proteins and alpha$_1$, alpha$_2$, beta, and gamma globulins and albumin-globulin (A/G) ratio, serum alkaline phosphatase, serum glutamic-pyruvic-transaminase, isocitric dehydrogenase, and serum bilirubin, each determined at same times as were hematologic values.) (Urinalysis included: pH, sp. gravity, sp. grav. concentration test, protein, reducing substances, glucose, ketones, bile pigments, bile salts, and urobilinogen determinations and, also, microscopic examination of the spun deposit for epithelial cells, polymorphonuclear leucocytes, mononuclear leucocytes, erythrocytes, organisms, casts, and other abnormal constituents.) Guthion had no effect on these values.

Neoplasms. None seen.

Organ Weight. No effect on weights of brain, pituitary, heart, lungs, liver, spleen, pancreas, thymus, kidneys, uterus/prostate, thyroids, adrenals, or gonads.

Histopathology. No effect. (Following tissues were examined: Spinal cord (lumbar and cervical enlargements), eye, sciatic and optic nerves, aorta, salivary gland, various levels of the alimentary tract (esophagus, stomach (2), duodenum, jejunum, ileum, colon (2)), gall bladder, urinary bladder, lymph nodes (cervical and mesenteric), skeletal muscle, skin and bone marrow.). No evidence of demyelination in CNS was seen.

"No-Effect" Level. 3 ppm (because of inhibition in RBC-ChE in dogs at 20 ppm). Overt no-effect level is 150 ppm.

Rabbit, reproduction study:

Thirty F New Zealand White rabbits, supposedly mated, were purchased. Each group of 10 received either 0, 5, or 25 ppm Guthion in the diet from the 8th through 16th day of gestation. Half the rabbits in each group were killed on the day before delivery, and fetuses and reproductive tract of mothers scanned for abnormalities. Rabbit fetal skeletons were examined after clearing and staining with alizarin red. Surviving rabbits were allowed to deliver and nurse young to weaning. These young were killed at 30 days and examined grossly.

FP No. OFO-869
FAP No. OH-2450

Results are tabulated:

Group A (killed before parturition)	ppm Guthion 0	5	25
No. mated	5	5	5
No. pregnant	4	3	4
No. of living fetuses	36	26	31
No. of dead fetuses	0	0	0
Avg. litter size	9	9	8
Group B (that delivered and nursed young)			
No. mated	5	5	5
No. pregnant	3	4	4
No. of young born alive	27	31	34
No. of young alive at 30 days	16	20	22
Avg. litter size	9	8	9

Gross Pathologic Observations in Group A Rabbits

Guthion in diet (ppm)	Average No. of Fetuses L.Horn	R.Horn	Sex M	F	Av.Wt. of Fetuses (g)	Length (Crown to Rump) (cm)	Average No. of Corpora Lutea L.Ovary	R.Ovary	Av. No. of Immature Fetuses
0	4.2	4.7	4.3	4.3	37.5	9.3	5.0	4.5	1
5	5.7	3.0	4.6	3.0	22.4	7.5	6.3	5.7	2
25	3.3	4.5	3.5	4.3	44.7	9.7	4.3	4.8	0

In gross examination of fetuses, the left hemidiaphragm was found absent in one II fetus from a rabbit in the 5-ppm group. Examination of cleared and stained skeletons disclosed a "vertrebral anomaly at C_4-T_4" in a II fetus from a rabbit on 25 ppm Guthion.

Comment:

This study shows no effect of up to 25 ppm Guthion on fertility of rabbits or on viability of fetuses, both at birth and at 30 days. (Death of so many of the young before this latter interval is attributed to the small cages used such that mother rabbits could not move without injuring offspring.) Nor is an effect of Guthion on litter-size shown.

The lesser weight of fetuses in the 5-ppm group is attributed to the number of immature fetuses present, not to an effect of Guthion. The relative distribution of fetuses in the uterine horns, the sex ration, and the numbers of corpora lutea detected were each comparable in rabbits in control and in Guthion-dosed groups.

Regarding the skeletal anomaly in the 25-ppm fetus, Petitioner states, "Although we have been unable to find reports of similar abnormalities in rabbit fetuses...both the type of anomaly and its incidence (1/31 fetuses examined in the 25-ppm group) suggest it was unrelated to presence of insecticide in the diet."

CONCLUSION:

For this study on reproduction (and teratogenesis) in the rabbit the "no-effect level" is, conservatively, 5 ppm; most likely, however it is as high as 25 ppm.

Summary:

These studies newly abstracted here have "no-effect levels," as follows:

Study	Based on ChE	Based on overt effect
Rat, 2-yr.-feeding:	5 ppm	50 ppm
Dog, 2-yr.-feeding:	5 ppm	150 ppm
Dog, 19-week-feeding	None established; lowest dose (20 ppm) caused inhibition.	20 ppm
Rabbit, teratogenic:	Conservatively, 5 ppm; probably 25 ppm	---

CONCLUSION:

Tolerances requested in this petition (and detailed in title) are safe.

H. Blumenthal per BJV 11-21-69

INIT: HBlumenthal

cc: SC-970
SC-470
SC-330
SC-310
VM-100
SC-900
PP No. 0F0-669, & 7F0-539
FAP No. 0H-2450

RQuaife:gr 11/20/69

Mouse reproduction study in 7F0539 fed F0, F1, and F2 generations.
[illegible] 2/16/70