

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
MALATHION

Chemical Code #: 000367; Tolerance #111
SB 950-343

July 30, 1986

Revised 2/23/87; 5/3/88; 10/2/89; 12/22/89; 4/5/90; 5/22/90; 9/5/90; 11/3/94; 11/18/96; 9/25/97

I. DATA GAP STATUS

| | |
|--------------------------------|---|
| Combined (chronic + onco) rat; | No data gap, possible adverse effect |
| Chronic dog: | No data gap, no adverse effect |
| Onco rat: | No data gap, no adverse effect |
| Onco mouse: | No data gap, possible adverse effect |
| Repro rat:: | No data gap, no adverse effect |
| Terato rat: | No data gap, no adverse effect |
| Terato rabbit: | No data gap, no adverse effect |
| Gene mutation: | No data gap, no adverse effect |
| Chromosome: | No data gap, no adverse effect |
| DNA damage: | No data gap, no adverse effect |
| Neurotox: | No data gap, no adverse effect ¹ |

1 - Studies performed in hen showed no adverse effect. Study performed in the rat show **possible adverse effect** for neurotoxicity.

Note, Toxicology one-liners are attached

** indicates acceptable study

Bold face indicates possible adverse effect

File name: T970925

Toxicology Summary by G. Chernoff, 9/5/90; M. Silva, 11/3/94, 11/18/96, 9/25/97.

Rectified through volume #: 220, record #: 155946

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

III. TOXICOLOGY ONE-LINERS AND DISCUSSION

COMBINED (CHRONIC + ONCO) RAT

**** 208 145994** "A 24-Month Oral Toxicity/Oncogenicity Study of Malathion in the Rat Via Dietary Administration," (Daly, I.W., Huntingdon Life Sciences, East Millstone, NJ; Study #: 90-3641; 2/27/96). Malathion (99.4% pure) was fed in diet to Fischer 344, CDF (F-344) CrIBR (90/sex/dose) at 0, 100/50 (reduced day 113), 500, 6000 and 12000 ppm for 24 months. Thirty-five/sex/dose (satellite) were sacrificed at 12 months. Systemic NOEL = 500 ppm (Mortality sharply increased in males at ≥ 6000 ppm and in females at 12000 ppm. Body weight was significantly decreased in males at ≥ 6000 ppm and in females at 12000 ppm. Effects were observed in hematology and clinical chemistry were observed in both sexes at ≥ 6000 ppm. Absolute and relative kidney and liver weights were significantly increased in both sexes at 12 and 24 months. Absolute and relative spleen (12 months) and thyroid/parathyroid (12 and 24 months) weights were increased in males at ≥ 6000 ppm. Histopathology showed an increase in nasal mucosal pathology in both sexes at ≥ 6000 ppm. Subacute-chronic inflammation/chronic nephropathy was increased in incidence and severity at 12 months in both sexes, primarily at 12000 ppm.) No evidence of ocular toxicity from ophthalmoscopic or electroretinographic examinations was observed. Absolute and relative kidney and liver weights were significantly increased in both sexes at 12 and 24 months. Absolute and relative spleen (12 months) and thyroid/parathyroid (12 and 24 months) weights were increased in males at ≥ 6000 ppm. Histopathology showed an increase in nasal mucosal pathology in both sexes at ≥ 6000 ppm. Subacute-chronic inflammation/chronic nephropathy was increased in incidence and severity at 12 months in both sexes, primarily at 12000 ppm.) ChE NOEL = 500 ppm (Plasma, erythrocyte and brain cholinesterase activity was significantly decreased, primarily at ≥ 6000 ppm.) Oncogenicity NOEL = 500 ppm (There was an increased incidence in hepatocellular adenomas and carcinomas in females at ≥ 6000 ppm. An increase in nasoturbinal adenoma was observed in males at ≥ 6000 ppm.) **Possible adverse effect.** Acceptable. M. Silva, 11/15/96.

**** 209 146414** "24 Month Oral Toxicity/Oncogenicity Study of Malaoxon in the Rat via Dietary Administration," (I.W. Daly, Huntingdon Life Sciences, Study No. 93-2234; April 2, 1996). Malaoxon (92.5% pure), was fed in diet to Fischer 344 rats (85/sex/dose) at 0, 20, 1000, or 2000 ppm for at least 24 months. Ten rats/sex/group (satellite) were sacrificed at 3, 6 and 12 months. Systemic NOEL = 20 ppm/day (There were increased deaths in both sexes at ≥ 1000 ppm. Emaciation at ≥ 1000 ppm (females) and at 2000 ppm (males) was observed. Decreased body weight and food utilization efficiency were observed in both sexes at 2000 ppm. Increased absolute and relative liver, kidney and adrenal weights occurred in males at 2000 ppm. Females showed decreased absolute and relative spleen weights at 2000 ppm. Histopathology showed increased chronic inflammation, epithelial hyperplasia and squamoid metaplasia in both respiratory and olfactory nasal mucosa in males at 2000 ppm and in females at ≥ 1000 ppm. In lung increased edema, interstitial inflammation, purulent and granulomatous inflammation were observed at ≥ 1000 ppm (males) and at 2000 ppm (females). Increased chronic inflammation in tympanic spaces occurred at ≥ 1000 ppm (males) and at 2000 ppm (females). Stomach muscularis mineral deposits were observed at ≥ 1000 ppm in both sexes.) No treatment-related effects on ophthalmology were reported. ChE NOEL = 20 ppm (Plasma, RBC and brain ChE were significantly decreased in both sexes at ≥ 1000 ppm.) Oncogenicity NOEL > 2000 ppm (There was no oncogenic effect due to malaoxon.) **ACCEPTABLE.** Possible adverse effect (Increased nasal, tympanic and lung pathology and decreased plasma, RBC and brain ChE were observed in both sexes.) (Kishiyama & Silva, 11/15/96).

220 155946 This volume contains a discussion of recently performed studies: 145/132086 (rat subchronic, inhalation), 208/145994 and 209/146414 (combined, rat with malathion and malaoxon, respectively) and 150/132499 (mouse oncogenicity) regarding how they compare with earlier studies. A weight-of-evidence classification of the oncogenic potential of malathion was considered. No worksheet. M. Silva, 9/19/97.

067 014771, "The Evaluation of the Chronic Toxicity Effects of Cythion Administered in the Diet to Sprague-Dawley Rats for 24 Consecutive Months", (Food and Drug Research Laboratories, Inc., Laboratory # 5436, 5/13/80), Malathion, 92.1%, Lot No. W70225-1; 50 Sprague-Dawley rats/sex/group were fed 0, 100, 1000 or 5000 ppm for 2 years; hematology at 12, 26, 53 and 104 weeks; sys NOEL = 100 ppm; chronic effects on liver and kidney by increased organ weight but this was not substantiated by microscopic findings; no oncogenic effect reported. **No adverse effect. Acceptable. These results differ from those of NCI below in which adverse effects on the GI tract were reported. Rereview finds that the initial review noting adverse effects in liver and kidney organ weight is not of biological significance in view of the pathology report in the supplemental submission, volumes 79-81. Document 111-097 contains a rebuttal dated 6/19/87. No change in status. (Gee, 8/5/85, 6/20/86 and 5/3/88)

EPA one-liner: Systemic NOEL = 100 ppm (decrease in body weight, decreased brain cholinesterase), systemic LEL = 1000 ppm, onco NOEL > 5000 ppm (HDT), guideline. In the February 1988, "Guidance for Reregistration...", EPA has reversed its decision and considers the study unacceptable upon reexamination due to deficiencies in data reporting, slide reading and intercurrent disease. A new study is being required in Fisher 344 rats. See 208/145994 for the new study.

079, 080, 081 037614, -15, -16, (Food and Drug Res. Lab., 1980). Addenda to 067 014771. Summary tables of organ weights, blood cholinesterase values, individual body weights and food consumption, histopathology report making reevaluation and upgrading of 014771 possible (Gee, 12/26/85).

088 051410, Addendum to 014771. Validation of analysis of fortified diets using 2 different detectors for GLC.

088 051411, Addendum to 014771. Analysis of diets by week plus stability data - upgrades Record # 014771 to acceptable.

CHRONIC RAT

022 024554, Summary only. Insufficient information to evaluate. Gee, 8/2/85.

007 024211, (Hazleton, 1952.) Summary only. Three formulations of malathion were given to 20 male rats/group at 500, 1000 or 5000 ppm. Survival data only over 109 weeks. **Unacceptable.** (Gee, 8/2/85)

EPA 1-liner: No CORE grade. Systemic NOEL = 1000 ppm (reduced food intake and weight gain), oncogenic NOEL > 5000 ppm (HDT), ChE NOEL = 100 ppm (LDT).

CHRONIC, DOG

098 058618, "One-Year Oral Toxicity Study in Purebred Beagle Dogs with AC 6,601", (Tegeris Laboratories, Inc., report # 85010, 2-10-87). AC 6,601, lot no. W40515-0011, 95.0%, was given to beagle dogs at 0, 62.5, 125 and 250 mg/kg/day by gelatin capsule, 7 days a week for 1 year, 6/sex/dose. No mortalities, no interim sacrifices. Systemic NOEL = 125 mg/kg/day, body weight depression, changes in hematological parameters and serum enzymes. ChE NOEL < 62.5 mg/kg/day. **No adverse effect. Acceptable. (Shimer, 2-23-88 and Gee 3/7/88)

EPA 1-liner: unacceptable because a NOEL was not established for increased liver and kidney weights, elevated platelet count, decreased creatinine, decreased BUN, inhibition of erythrocyte and plasma cholinesterases. A new study is required - see "Guidance for the Reregistration of Pesticide Products containing Malathion as an Active Ingredient", February, 1988.

Note: In a conversation with Dr. B. Dementi of EPA, CDFA was informed that EPA is no longer requiring a new study with non-rodents at this time. (Gee, 4/6/90)

ONCOGENICITY, RAT

068 014772, "Bioassay of Malathion for Possible Carcinogenicity", (NCI conducted at Gulf South Research Institute, report # (NIH) 78-824, December 1977), Malathion, >95% purity, lot SPS-10127; Osborne-Mendel rats; 10/sex in controls plus 40/sex pooled controls (from other studies conducted within the year at Gulf South Res. Inst.) and 50/sex/test group were fed 0, 4700 or 8150 ppm (TWA) for 80 weeks and observed for 33 -- initial doses were 8000 and 12000 which were decreased at week 14 for low dose group to 4000 ppm and at week 3 for the high dose group from 12000 to 8000 ppm for 77 weeks. **Unacceptable** (no hematology, inadequate number of controls and no historical control data, problems with dose selection and drastic changes in dose part way through study, missing data); not clear whether an oncogenic effect. A later volume, 111-086, contains a published article in Environmental Research 37: 154-173 (1985), record #041972, reviewing the pathological findings of this and 2 other NCI-sponsored onco studies. The authors conclude that malathion had no effect on survival of Osborne-Mendel rats. They also concluded that no evidence of carcinogenicity was found. The review by Remsen (Gee) indicated an oncogenic effect in the thyroid of male rats. The reexamination of the slides resulted in the finding of an additional adenoma in the pooled control and one in the low dose group so the incidence as reported in the cited publication in males is: follicular cell adenoma/carcinoma -- 1/14, 1/14 (control), 6/41, 2/41 (low dose) and 7/35, 2/35 (high dose); C-cell adenoma/carcinoma - 1/14, 0/14 (control), 3/41, 0/41 (low dose) and 1/35, 0/35 (high dose). By Fisher's exact test, the P value for the combined adenomas/carcinomas is 0.22 for high dose compared with control incidence. Therefore, the original finding of oncogenicity is no longer evaluated as significant in view of the added information. Due to lack of individual data in the NCI report, it is not possible to identify either when or in which rats the findings were made. Also, the numbers in the publication do not match those in the NCI report for thyroid findings even considering the added two adenomas. The numbers reported by NCI are:

| Thyroid | Control | low dose | high dose |
|---------------------------|---------|----------|-----------|
| follicular-cell adenoma | 1/5 | 1/41 | 1/47 |
| follicular-cell carcinoma | | 2/41 | 6/47 |
| C-cell adenoma | | 1/41 | 3/47 |

Report does not indicate any effect(s) on the stomach. NOEL cannot be determined accurately due to dosage changes but on the basis of body weight using the TWA, the NOEL would be 4700 ppm. **No adverse effect.** Document 111-097 contains a rebuttal dated 6/19/87. No change in status. (Gee, 8/9/85 and 5/3/88)

EPA one-liner: onco NOEL > 8150 ppm (HDT), minimum.

086 041972, (Publication in Environmental Res. 37: 154-173 (1985) by Huff, J. E. et al.). Paper addresses the pathology of three NCI/NTP onco studies in the 1970's with reevaluation of the slides. Using the data presented in this publication, the rereview of the studies has resulted in some changes in the findings originally stated by Remsen (Gee) in 014772, 014773 and 024193. (Gee, 6/19/86)

068 014773, "Bioassay of Malathion for Possible Carcinogenicity", (NCI, No. 192, Publication No. 79-1748, conducted at Gulf South Research Inst., 1979), Malathion, 95% purity, lot SPS-10127; 50 F344 rats/sex/group were fed 0, 2000 or 4000 ppm for 103 weeks; dose selection based on 13-week study from 0 - 16,000 ppm with 100% survival at 8000 ppm; decreased body weight in males only and decrease in survival at 4000<2000<control from toxicity. **Adverse effects:** Positive for chronic effects on gastrointestinal tract (forestomach: chronic inflammation, ulcers, others); the possible oncogenicity in the adrenals (pheochromocytoma) is not clear as the incidence is not dose dependent and occurred in males only at 2/49 (control), 11/49 (low dose) and 6/49 (high dose). A publication in Environmental Research 37: 154-173 (1985), 111-086, #041972, addressed the issue in a reexamination of the pathology slides and concluded that there was no oncogenicity effect but confirmed the chronic effect on the stomach. The number of animals, however, does not agree between the publication and the Report 192. The trend, however, is the same. In conclusion, the report shows a chronic effect with doubtful oncogenic effects. **Unacceptable** with missing individual data, doubtful high dose for females especially. Not upgradeable. NOEL < 2000 ppm. (Remsen, 8/9/85)
EPA one-liner: onco NOEL > 4000 ppm (HDT), Systemic NOEL < 2000 ppm, minimum.

058 034788, "Bioassay of Malaoxon for Possible Carcinogenicity", (NCI, No. 135, NIH publ. no. 79-1390, conducted at Gulf South Research Inst., 1979), Malaoxon analog of malathion, >95% purity; 50 F344 rats/sex/group were fed 0, 500 or 1000 ppm for 103 weeks; diet analyzed as within 2% of target ppm; dose selection based on subchronic study. Summary data only presented and no individual data, no third dose, no cholinesterase measurements, no hematology; equivocal evidence for oncogenicity in male and female F344 rats for C-cell adenoma/carcinomas in thyroid; positive for chronic toxicity to the gastrointestinal tract with dose-related increased incidence in ulcers of the forestomach with male rats being more sensitive than females. A publication (111-086, 041972) addresses these findings in a reexamination of the pathology slides from this and two other studies. The numbers in 041972 do not agree with those in this report although the trend is the same.

| Thyroid | | Control | low dose | high dose |
|-----------------|---|---------|----------|-----------|
| C-cell adenoma/ | M | 2/49 | | 4/49 |
| Carcinoma | F | | 1/49 | 5/47 |
| Reexam | M | 3/49 | 3/45 | 10/49* |
| | F | 4/48 | 7/48 | 11/48* |

The values from this report are not significant by Fisher exact in males but are in females. The reexam values are significant in both sexes. The publication does not discuss why the numbers are so different. In conclusion, malaoxon shows chronic toxicity and marginal oncogenicity as does malathion. NOEL < 500 ppm (body weight, behavior). **Unacceptable.** (Gee, 8/6/85)
EPA 1-liner: Minimum. Oncogenic NOEL > 1000 ppm (HDT). EPA is requiring a new study in the Fisher 344 rat with malaoxon to clarify the results in the above study - see February, 1988, "Guidance for the Reregistration...."

****SUMMARY:** Based on the new studies, it is concluded that malathion is possibly oncogenic in the rat, with increased hepatocellular adenomas and carcinomas in females and nasoturbinal adenomas in males observed at \geq 6000 ppm. Malaoxon, however, was not oncogenic in rat. In mouse adenomas occurred with increased incidence at 8,000 and 16,000 ppm. Chronic effects were observed primarily in the liver and at doses greater than or equal to doses at which adenomas/carcinomas occurred. (M. Silva, 11/27/96).

ONCOGENICITY, MOUSE

****150 132499** "18-Month Oral (Dietary) Oncogenicity Study in Mice," (Slauter, R.W., IRDC, Mattawan, MI, Project ID: 668-001, 10/12/94). Malathion technical (96.4% pure) was fed (in diet)

to B6C3F1BR mice (65/sex/dose) at 0 (acetone, used in blending), 100, 800, 8,000 and 16,000 ppm for 18 months (with a 12 month interim kill; 10/sex/dose). **Systemic NOEL = 800 ppm** (There was decreased body weight gain and decreased food consumption in both sexes at \geq 8000 ppm. Absolute and/or relative weight decreases were observed in brain, heart, kidney & spleen at \geq 8000 ppm. Absolute and/or relative weight increases were observed in liver (both sexes) and testes (males) at \geq 8000 ppm. Macro & histopathology was increased in liver at \geq 8000 ppm in both sexes.) **ChE NOEL = 100 ppm** (Plasma ChE was significantly decreased in males at \geq 8000 ppm & in females at \geq 800 ppm. RBC ChE was significantly decreased in both sexes at \geq 800 ppm. Brain ChE was decreased in both sexes at 16000 ppm.) **Possible adverse effect: Oncogenicity NOEL = 800 ppm** (There was an increase in liver adenomas, adenomas + carcinomas and hypertrophy in both sexes at \geq 8000 ppm.) Acceptable. M. Silva, 10/24/94.

068, 104 034789, 069632, "Bioassay of Malathion for Possible Carcinogenicity", (NCI conducted at Gulf South Research Institute, report # (NIH) 78-824, December 1977), Malathion, \geq 95% purity, lot SPS-10127, identity of compound was verified by Gulf South Res. Inst., 10/sex for concurrent control and 50/sex/group for test were fed 0, 8000 or 16000 ppm for 80 weeks followed by 14 weeks observation; B6C3F1 mice. Oncogenic effect in liver of males at 16000 ppm. NOEL < 8000 ppm (body weight). Originally reviewed (Gee 8/9/85) unacceptable but possibly upgradeable with submission of missing data on histopathology, and as having a possible adverse effect (male liver oncogenic effect). Risk assessment by CDFA Medical Toxicology (T.R. Hathaway, 7/31/87) found the liver effect to not be of biological significance, hence, **no adverse effect indicated. Subsequently reviewed (Gee 5/3/88) with no status change. Re-reviewed with submission of individual histopathology data (# 069632). **Status change to acceptable.** (Green and Silva, 8/28/89)

EPA one-liner: Onco NOEL > 16,000 ppm (HDT--questionable liver findings-not significant with Bonferroni criteria. However, related trench [sic] [$p = 0.019$] and increase of tumors at high dose [$p = 0.031$] - a level EPA normally considers significant), minimum.

058 034788, "Bioassay of Malaoxon for Possible Carcinogenicity", (NCI, No. 135, 1979, NIH publ. no. 79-1390, conducted at Gulf South Research Institute). Malaoxon analog of malathion, > 95% purity, 50 B6C3F1 mice/sex/group were fed 0, 500 or 1000 ppm for 103 weeks; dose selection based on a subchronic study - data not included; NO evidence of oncogenicity is reported.

Unacceptable with no individual data, two doses only, no hematology, marginal chronic toxicity at high dose on body weight, etc., so questionable if adequate. The initial review indicated chronic toxicity was reported. Rereview of the study (Gee, 6/19/86) now indicates the findings of behavior modification and mortality are not of biological significance, the latter only indicating adequacy of dose level. NOEL: 500 ppm. **No adverse effect.** (Gee, 8/6/85 and 6/19/86)

EPA one-liner: onco NOEL > 1000 ppm (HDT), systemic NOEL < 500 ppm (decreased mean body weights in F), minimum. No additional data are required.

REPRODUCTION, RAT

083, 088 037620, 051409, "Report on Malathion: Successive Generation Studies with Rats, Final Report", (American Cyanamid Co., report # 68-64, 7/9/68), Malathion, 95% purity, SPS-6111; data on F2 breeding for F3 generations only - not on other generations; approximately 16 matings at each dose of 0, 100, 500 or 2500 ppm fed in the diet. Use of cedar shavings resulted in respiratory problems in F3b pups; reproduction, lactation, necropsy and histopath data for F3 pups; positive **adverse effect** identified for decrease in lactation index. Systemic NOEL = 500 ppm (decreased body weight), repro NOEL = 500 ppm (decreased lactation index).

Unacceptable (no interim pup weights - days 1, 4, 7 or 14, no necropsy on adults, no analysis of diet, intercurrent disease, husbandry problem, single body weight for adults prior to mating only), not upgradeable. Document 111-097 contains a rebuttal dated 6/19/87. No change in status. (Gee, 12/26/85 and 5/3/88)

EPA is requiring a new reproduction study. The above study is considered unacceptable based

on insufficient number of animals, lack of individual data and other deficiencies - see February, 1988, "Guidance for the Reregistration...."

126 091230, "A Two-Generation (Two Litters) Reproduction Study with AC 6,601 to Rats", (R.E. Schroeder, Bio/Dynamics Inc., Report 87-3243, June 28, 1990). Malathion, 94% purity, lot #AC6015-136, was administered in the diet to groups of 25 male and 25 female rats at dose levels of 0 (vehicle control), 550, 1700, 5000, or 7500 ppm for two generations, two litters per generation. At 7500 ppm, maternal gestational and lactation weights were consistently reduced in both litters of both generations, with statistical significance being obtained in the first pregnancy and both lactation periods of the P-1 generation. Pup weaning weights on day 21 post partum were consistently reduced at both 5000 and 7500 ppm, reaching statistical significance for all litters at 7500 ppm, and the first P-1 and second F-1 litters at 5000 ppm. At 7500 ppm, the postnatal growth retardation persisted through adulthood, with no indication of catch-up growth. Reproductive parameters were not adversely effected. Developmental NOEL = 1700 ppm; > 200 mg/kg/day (postnatal growth retardation); Parental NOEL = 5000 ppm; > 400 mg/kg/day (reduced body weight); Reproductive NOAEL = 7500 ppm (HDT); > 600 mg/kg/day. The study is **ACCEPTABLE, and no adverse reproductive health effect is noted (G. Chernoff, 8/23/90).

SUMMARY: In the initial unacceptable rat reproduction study (record #'s 037620 and 051409), a decrease in the lactation index at 2500 ppm was identified as a possible adverse health effect, with a NOEL = 500 ppm. This outcome was not replicated in the acceptable two generation, two litters per generation repeat study (record # 091230). Given the superior quality of the repeat study, along with the failure to replicate the earlier reported adverse effect, the finding of the acceptable study, no potential adverse reproductive health effects, should be used for risk assessment purposes (G. Chernoff, 9/30/90).

TERATOLOGY, RAT

111 074764, "A Developmental Toxicity Study With AC 6,601 in Rats", (Argus Research Laboratories, Inc., Laboratory Project ID 101-005, 4/5/89). AC 6,601 (malathion), technical grade, purity 94.0%, was administered to groups of 25 CrI:CD (SD) BR female rats by gavage on days 6 through 15 of gestation at doses of 0 (corn oil vehicle control), 200, 400 or 800 mg/kg/day. The only significant finding in the dams was an increased incidence of urine stained abdominal fur at 800 mg/kg/day. Fetal parameters were unaffected by treatment and no adverse effect was noted. Maternal and Developmental NOEL = >800 mg/kg/day (the high dose tested). Originally reviewed as unacceptable (Kishiyama & Chernoff, 12/89), but with the submission of the dose justification in CDFA Record No. 090478, the study is upgraded to **ACCEPTABLE (G. Chernoff, 4/5/90).

111 074765, Supplement to 074764; dosing solution analyses. No Worksheet.

118 090478, Pilot study for dose justification in record no. 074764.

068 014778, "Teratogenicity Studies on Linuron, Malathion and Methoxychlor in Rats", (Bureau of Chemical Safety, Canada, 8/25/77, Publication in Toxicol. Appl. Pharmacol. 45: 435-444 (1978), accepted in 1977, Khera, K. S. et al.), Malathion technical, no purity stated; 20 Wistar rats/group were given 0, 50, 100, 200 or 300 mg/kg by oral gavage, days 6-15 of gestation. **No adverse effect** on reproduction or teratogenic effect is reported. Sacrificed on day 22 with 2/3 of fetuses for skeletal exam and 1/3 for visceral. One table only. **Unacceptable** (inadequate high dose) Sys NOEL > 300 mg/kg/day (HDT), Dev. toxicity NOEL \geq 300 mg/kg/day. (Gee, 8/9/85)

092 053281, Duplicate of publication, Record # 014778, plus copies of raw data for malathion. Includes mating identification, individual body weights and litter findings. Data from range-finding study to 600 mg/kg/day - 4 per group.

TERATOLOGY, RABBIT

089 051413, "A Teratology Study with AC 6,601 in Rabbits", (Food and Drug Research Laboratories, Inc., study # 8171, 2/28/85). Malathion, 92.4%, was administered by gavage to groups of 20 inseminated New Zealand rabbits at doses of 0, 25, 50 or 100 mg/kg/day on day 6-18 of gestation. Maternal weight gain during dosing was statistically reduced at 50 and 100 mg/kg/day. Mean numbers and percent fetal resorptions were also elevated at these two doses. The number of unexplained unscheduled deaths were elevated above historical control values in the low dose group, but did not achieve statistical significance. In addition, there was no evidence for a dose response effect. Maternal NOEL = 25 mg/kg/day (reduced weight gain during dosing); Developmental NOEL = 25 mg/kg/day (increase in resorptions). The study is **ACCEPTABLE, and no adverse developmental health effects are noted (Parker, 2/13/87; Chernoff, 9/3/90). EPA has accepted this study.

GENE MUTATION

068, 099 014776, 060150, "Microbiological Assays in: In vivo and in vitro Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens", (SRI for EPA, project LSU-3493, February 1977). Malathion, technical grade, 92-97% purity, lot # 40216006.300; tested in Salmonella typhimurium strains TA1535, TA1537, TA1538 and TA100 (no TA98), single plate, several trials with and without activation at 0, 1, 5, 10, 50, 100, 500 or 1000 ug/plate. **No increase in reversion rate** is reported. 060150 contains individual plate counts. **Unacceptable** (lacks TA98, some positive controls). (Gee 8/9/85 and 3/3/88)

067 014770, "Mutagenicity Testing of Cythion Malathion in the Ames Bacterial Test", (American Cyanamid Co., 6/2/78). Malathion, 92.8% purity, Salmonella typhimurium strains TA 1535, TA1537, TA98 and TA100 with and without activation at 0, 10, 100 and 1000 ug/plate; also E. coli WP2. **Unacceptable** (too few plates, concentrations, inadequate controls). **No adverse effect** reported. Some suggestion of cytotoxicity at 1000 ug/plate. (Gee 8/2/85)

157-009 034551, "The Mutagenic Effect of Organophosphate Insecticides on Escherichia coli", (Tunstall Laboratory, 8/71). Malathion technical, 97.4% purity, tested at an unspecified amount with E. coli B/r WP2 strain for tryptophan reversion in triplicate; result reported as "-". **Unacceptable**, no data. (Gee 2/20/87)

122 086717, "Evaluation of CL 6,601 in the Bacterial/Microsome Mutagenicity Test", (Traul, K. A., American Cyanamid Company, Agricultural Research Division, Study No. 114, 3/9/87). Malathion (CL 6601, batch AC 4870-54B, 95.2% purity) was tested by the plate incorporation assay with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 as well as with Escherichia coli strain WP2 uvrA-. Concentrations tested were 0 (DMSO), 100, 500, 1000, 2500 or 5000 ug/plate with triplicate plates per concentration and two trials. Bacteria were plated with and without activation with S-9 prepared from livers of male Sprague-Dawley rats and purchased from Microbiological Associates. Positive controls with and without activation for each strain were effective. No increases in revertants with any strain were reported. **No adverse effect. Acceptable. (Gee, 5/18/90)

**SUMMARY: Although each study has deficiencies in design or reporting of data, when examined collectively the studies provide sufficient information to determine that malathion is not mutagenic in bacteria. The data gap is, therefore, filled for the gene mutation test type. (Gee, 1987) The most recent submission (Record 086717) is acceptable independent of the other studies and confirms the negative results. (Gee, 5/90)

CHROMOSOME EFFECTS

068, 099, 108 014774, 060282, 073931, "Dominant Lethal Test in the Mouse," (SRI for EPA, project LSU-3493, February, 1977). Malathion, technical grade, 92-97% pure was fed in the diet for 7 weeks to 20 ICR/SIM male mice/group at 0, 1250, 2500 or 5000 mg/kg, before the animals were mated 1:2 for one week over 8 intervals. **No evidence of a dominant lethal effect reported. Record 060282 contains the individual data and a statement addressing the purity of the technical malathion. Previously reviewed as unacceptable (Gee, 12/27/85 & 3/3/88), the study has been upgraded to **acceptable** with submission of the requested diet analysis. (M. Silva, 8/28/89.)

085 037622, Addendum with summary data by mating week for 014774.

068 014777, "Genetic and Cytogenetic Effects induced in the Mouse by an Organophosphorus Insecticide: Malathion", (Publication in Environmental Res. 34: 170-174 (1984) by Degraeve and Moutschen.), Malathion, > 99% purity, Q-strain male mice (number not stated) were given 0 or 300 mg/kg i.p. with 12, 24 or 36 hour recovery periods; 500 metaphases from bone marrow and varying number of spermatogonia were analyzed for aberrations. **No adverse effect** is reported in the publication. **Unacceptable** as is - need the full report. (Gee, 8/9/85)

122 086718, "Acute Test for Chemical Induction of Chromosome Aberration in Rat Bone Marrow Cells in vivo with AC 6,601", (Gudi, R., SITEK Research Laboratories, Rockville, MD, #0125-1531, 3/22/90). Malathion (AC 6,601, batch AC6015-136B, 94%) was given by oral gavage to Sprague-Dawley rats as a single dose. Based on a preliminary trial, doses selected were 0 (corn oil), 0.4, 0.8 and 1.6 ml/kg, equivalent to 0.5, 1.0 and 2.0 g/kg based on density of 1.25. There were 5/sex/group for the definitive assay with sacrifices at 12, 24 and 48 hours post-treatment. Mitotic indices as well as aberrations were scored. Fifty cells per animal per sex per group were evaluated for aberrations excluding gaps. There was no effect on the incidence of aberrations and only a possible slight decrease in the MI at 24 and 48 hours in the high dose groups. **No adverse effect. Acceptable. (Gee, 5/18/90)

DNA DAMAGE

068, 099 014775, 060284, "Mammalian in vitro Unscheduled DNA Synthesis Assays", (SRI for EPA, project no. LSU-3493, February 1977). Malathion, technical grade, 92%-97% purity, unscheduled DNA synthesis in human diploid fibroblasts WI-38, passage 28, tested with and without activation, cells were exposed for 3 hours in the presence of tritiated thymidine to 0, 10^{-7} , 10^{-6} , 10^{-5} , 10^{-4} , or 10^{-3} M, 6 flasks without activation and 3 with activation; No cytotoxicity reported except possibly at the highest concentration. **No evidence for unscheduled DNA synthesis is reported as increased DPM/ug DNA. Initially reviewed as unacceptable based on the lack of sufficient details in the protocol and information on the test material. Record # 060284 contains the detailed protocols including passage number of the WI-38. The study is upgraded to **acceptable** status with the supplementary information. (Gee, 8/9/85 and 3/3/88)

068 034790, "Microbiological Assays in: In vivo and in vitro Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens", (SRI for EPA, project LSU-3493, February 1977), Escherichia coli. Malathion, no purity stated, 0 or 1 mg added to a disc on plates with E. coli W3110 or p3478 -- also with Bacillus subtilis strains H17 and m45. Zones of inhibition were measured. **No difference in growth between repair defective and repair effective strains.** **Unacceptable** (no justification for single concentration, single value only although report indicates three trials), because no cytotoxicity was demonstrated, the result is a "no test." (Gee, 8/9/85)

068 034791, "Microbiological Assays, in: In vivo and in vitro Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens", (SRI for EPA, project LSU-3493, February 1977). Summary data only. Malathion, no purity stated; Saccharomyces cerevisiae strain D3 measured for mitotic crossing-over at 50 mg/ml (5%) with and without activation, 4 hour exposure. **No adverse effect** reported. **Unacceptable** due to missing information. (Gee, 8/9/85)

122 086716, "Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocyte Cultures by Autoradiography with AC 6,601", (Pant, K. J., SITEK Research Laboratories, Rockville, MD, 1/24/1990, Study No. 0125-5100). Malathion (technical, batch AC 6,601, 94%) was tested with primary hepatocytes from male Sprague-Dawley rats. After a preliminary range-finding assay, the concentrations used in the UDS assay were 0 (DMSO, untreated or ethanol), 0.02, 0.04, 0.08, 0.12 or 0.16 ul/ml with an 18 hour incubation in the presence of 10 mCi/ml ³H-thymidine. Incorporation of thymidine into nuclei was quantitated by autoradiography with 150 nuclei per concentration scored in morphologically normal cells in the 0.02 through 0.12 ml/ml groups. The positive control was 2-AAF and that treatment gave the anticipated results with 100% of nuclei having ≥ 5 net grains. Treatment with malathion did not induce an increase in unscheduled DNA synthesis. **No adverse effect with hepatocytes. **Acceptable.** (Gee, 5/18/90)

NEUROTOXICITY

103 068075, "42-Day Neurotoxicity Study with AC 6,601 Technical in Mature White Leghorn Chickens", (Bio-Life Associates, Ltd., report # 87 DN 109, 4/1/88). AC 6,601 Technical (malathion), 93.6% purity, administered by gavage with protection (intramuscular injection of atropine sulfate at 10.0 mg/kg) at 1007.5 mg/kg to 60 hens. Survivors (21 hens) were redosed with protection at 852.5 mg/kg on day 21. Negative control (1.87 ml and 1.15 ml of tap water on day 1 and day 21 respectively) and positive control (TOTP at 500mg/kg) groups of 15 hens. 39 of the 60 hens dosed on day 1 at 1007.5 mg/kg died by day 15, the remaining 21 birds survived through day 21. 7 of the 21 birds re-dosed at 852.5 mg/kg on day 21 died by day 28. 14 survived through day 42. Reversible moderate/severe ataxia to paralysis of legs and wings and inability to stand reported in all malathion treated hens through day 4 and again, after redosing on day 21, through day 25. 10 hens/group for histopathology -unremarkable for malathion treated group. **No adverse effect. Acceptable. (Green and Silva 8/28/89)

** **144 132081** "An Acute Neurotoxicity Study of Malathion in Rats," (Lamb, I.C., WIL Research Laboratories, Inc., Ashland, OH, 3/2/94). Malathion technical (96.4% pure) was administered by gavage in a single dose (volume = 5 ml) to Sprague-Dawley Crl:CD BR rats (27/sex/dose) at 0 (vehicle = corn oil), 500, 1000 or 2000 mg/kg. Dosing was followed by a 15 day observation period. Systemic NOEL = 500 mg/kg (The FOB showed an increase in salivation on day 0 at ≥ 1000 mg/kg in both sexes and in females on day 7 at 2000 mg/kg. Males showed red deposits on nose & eyes at 2000 mg/kg and on mouth at ≥ 1000 mg/kg on day 0. Females had red deposits on eyes day 14 at 2000 mg/kg. Males showed very soiled/crusty fur and pale mucous membranes day 0 and females had crusty deposits on mouth day 14. There was a significant decrease in rotarod performance for males on day 14 at 2000 mg/kg. Males had decreased ambulatory and total motor activity at 2000 mg/kg. Females had decreased absolute & relative midbrain values and increased relative whole brain, brain stem & cerebral cortex weight values on day 15 at 2000 mg/kg. Males at 2000 mg/kg (day 7) showed relative olfactory region weight increases. At 2000 mg/kg males had lumbar root axonal degeneration, lumbar dorsal fiber digestion chambers, tibial nerve digestion chambers & retinal rosette formation.) ChE NOEL = 500 mg/kg (Both sexes at 2000 mg/kg showed decreased RBC & plasma ChE. Males showed some decrease in brain ChE at ≥ 1000 mg/kg.) **Possible adverse effect: Both sexes showed neurotoxicity at 2000 mg/kg.** Acceptable. The data are currently supplemental. M. Silva, 10/3/94.

145 132083 "A Subchronic (13-Week) Neurotoxicity Study of Malathion in Rats," (Lamb, I.C., WIL Research Laboratories, Inc., Ashland, OH; WIL-206006, 6/9/94). Malathion technical (96.4% pure) was fed in diet to Sprague-Dawley CrI:CDBR rats (25/sex/dose) at 0 (diet), 50, 5000 and 20000 ppm for 91 consecutive days. **Systemic NOEL = 5000 ppm** (Clinical effects were observed in both sexes at 20000 ppm. Body weights and food consumption were significantly decreased at 20000 ppm. Males (1/5) had digestion chambers in the lumbar dorsal root fibers and the peroneal nerve at 20000 ppm. Another 1/5 males had swollen axons and demyelination in the sciatic nerve at 20000 ppm. These were the only findings. Relative brain & brain region weights were increased (relative to body weights) in both sexes and cerebellum weights were decreased in females (relative to brain weights) at 20000 ppm.) **Neurological NOEL = 5000 ppm** (Both sexes showed an increase in soiled fur and females showed red deposits on the nose at 20000 ppm. Forelimb grip strength was decreased at 20000 ppm in both sexes.) **ChE NOEL = 50 ppm** (Plasma and RBC ChE was significantly decreased in both sexes at \geq at 5000 ppm. Brain ChE was significantly decreased in both sexes at 20000 ppm.) Acceptable, however, these data are currently supplemental. **Possible adverse effect for neurotoxicity.** M. Silva, 11/2/94.

145 132086 "A 13-Week Toxicity Study of Aerosolized Malathion Administered by Whole-body Inhalation Exposure to the Albino Rat," (Beattie, G., Bio-Research Laboratories, Inc., Quebec, Canada, Project ID#: 90729, 3/16/94). Malathion technical (96.4% pure, Lot #: 01112-00) was administered in air to Sprague-Dawley CD [CrI:CD(SD)BR] rats (15/sex/dose) at 0 (room air), 0.10, 0.45 and 2.0 mg/L (whole body exposure, 6 hours/day, 5 days/week) for 13 weeks. A systemic NOEL was not achieved (Clinical signs were increased in both sexes at all doses. Males had significant increases in organ/BW% in liver, lungs/trachea & kidney at 2.0 mg/L and in organ/brain wt% in liver and kidneys at 2.0 mg/L. Males also had a significant increase in lungs/trachea & kidney weights at 2.0 mg/L. Females showed a significant increase in organ/BW% in liver at \geq 0.45 mg/L and a significant increase in relative (to brain weight) weight at 2.0 mg/L. **Possible adverse effect:** The nasal cavity showed an increase in degeneration and/or hyperplasia of the olfactory epithelium at all treatment levels in both sexes.) ChE NOEL = 0.1 mg/L (Males showed a significantly decreased brain ChE at 2.0 mg/L. RBC ChE was reduced significantly in males at \geq 0.45 mg/L. Females showed a significantly decreased brain ChE at 2.0 mg/L. RBC ChE was significantly decreased at 0.45 mg/L and 2.0 mg/L. Plasma ChE was significantly decreased at 2.0 mg/L.) These data are supplemental. M. Silva, 10/27/94.

SUPPLEMENTAL STUDIES

121 086381, "Disposition and Metabolism of ^{14}C -Labeled Malathion in Rats (Preliminary and Definitive Study)", (Reddy, V., T. Freeman and M. Cannon, Midwest Research Laboratories, Project No. 9354-B, 12/20/89). Malathion (unlabeled at 94.6% and ^{14}C -labeled at 98%) was given by oral gavage to 5/sex/group of Sprague-Dawley (CrI:CD BR) rats at single doses of 40 or 800 mg/kg or 15 doses of unlabeled malathion at 40 mg/kg followed by a 16th dose of radioactive malathion. Excretion was followed for 72 hours before sacrifice of the animals and measurement of tissue content. Most of the malathion was excreted in the first 12 hours predominantly in the urine of both males and females. Less than 1% was retained in the tissues with the level in the liver being the highest. Ten metabolites were identified by GC/MS of material eluted from HPLC. The major metabolites were the a and b isomers of the monocarboxylic acid derivative and the dicarboxylic acid derivative of malathion. The intravenous route was not used due to the insolubility of malathion in water or saline. Report is complete and acceptable. (Gee, 5/21/90)