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

MEMORANDUMOFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Malathion

FROM: Kerry L. Dearfield, Ph.D. *Kerry L. Dearfield*
Executive Secretary, Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Joanne Edwards
Review Manager
Special Review and Registration Division (H7508C)

The Health Effects Division Peer Review Committee met on February 7, 1990 to discuss and evaluate the weight-of-the-evidence on Malathion with particular reference to its carcinogenic potential. The Committee agreed to classify malathion as a Group D Carcinogen; that is, malathion is not classifiable as to human carcinogenicity. This decision was based on the inadequacy of the available studies to make a definitive determination of the carcinogenicity of malathion. The Committee reaffirmed the requirements of the Malathion Registration Standard that requires the Registrant to perform an additional mouse carcinogenicity study with malathion and an additional rat carcinogenicity study with malaoxon. The Committee also determined that the Registration Standard recommendation to perform a carcinogenicity study in combination with the required rat chronic study on malathion be made into a requirement that both be performed.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Penelope A. Fenner-Crisp

William L. Burnam

Karl Baetcke

Marcia Van Gemert

*Penelope A. Fenner-Crisp**Wm L. Burnam**Karl Baetcke**Marcia van Gemert*

John Quest

John A. Quest

Esther Rinde

Esther Rinde

Kerry Dearfield

Kerry Dearfield

Richard Levy

Richard Levy

Marion Copley

Marion Copley

George Ghali

G. Ghali

Richard Hill

Richard Hill

Robert Beliles

Robert Beliles

Julie Du

Julie Du

Yin-Tak Woo

Yin Tak Woo

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Brian Dementi

Brian Dementi, R.D., 3/22/90

Roger Gardner

Roger Gardner 3/22/90

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Reto Engler

Reto Engler

4. Other Attendees:

Bruce Jaeger, HED
Bernice Fisher, HED
Hugh Pettigrew, HED
Linda Kutney, HED

B. Material Reviewed:

The material available for review consisted of 1) a draft Toxicology Branch I response to the Registrant's technical response to the Malathion Registration Standard; 2) selected pages from the Malathion Registration Standard (issued February, 1988); 3) reviews of carcinogenicity studies on malathion and malaoxon (consisting of memoranda and DER's); 4) journal publication Huff et al. (Environ. Res. 37: 154-173, 1985) on the National Toxicology

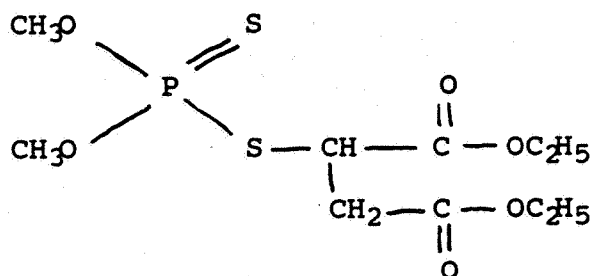
Program (NTP) reevaluation of malathion and malaoxon National Cancer Institute (NCI) rat carcinogenicity studies; 5) memorandum of E. McConnell, D.V.M. to J. Moore, D.V.M., June 14, 1984 with attached Summary Minutes of the NTP's Board of Scientific Counselors review of malathion; this is a status report on the NTP review of NCI malathion carcinogenicity studies; and 6) memorandum from A. Gross, Ph.D. (April 24, 1984) concerning the carcinogenicity of malathion.

This package was prepared by Brian Dementi, Ph.D., of Toxicology Branch I, Health Effects Division. The discussion on each of the individual carcinogenicity studies follows the presentations by Dr. Dementi. The material reviewed is attached to the file copy of this report.

C. Background Information: A chemical name for malathion is S-[1,2-bis(ethoxycarbonyl)ethyl]-O,O-dimethyl phosphorodithioate. In one of the submitted carcinogenicity studies, it is also named Cythion. Malathion is an organophosphate insecticide and miticide. It is used on a wide variety of food and non-food crops as well as for insect control for both outdoor and indoor situations. Its mode of activity is through cholinesterase inhibition. There are several basic producers of malathion in the United States.

The Chemical Abstracts Service (CAS) Registry number for malathion is 121-75-5 and the Tox Chem Number (or Caswell number) is 535. The CAS Registry number for malaoxon (this oxygen analogue of malathion is considered the active metabolite of malathion; the double bonded S in malathion is replaced by a double bonded O in malaoxon) is 1634-78-2.

Structure of Malathion:



D. Evaluation of Carcinogenicity Evidence for Malathion:

There were four carcinogenicity studies reviewed using malathion as the test chemical (total of three rat studies using Osborne-Mendel, Fischer 344 and Sprague-Dawley rats and one in B6C3F1 mice). There were two carcinogenicity studies reviewed using malaoxon as the test chemical (one in Fischer 344 rats and one in B6C3F1 mice).

1. Malathion - Osborne-Mendel Rat Dietary Feeding Carcinogenicity Study

Reference: National Cancer Institute. 1978. Bioassay of malathion for possible carcinogenicity, CAS No. 121-75-5. Technical Report Series, No. 24, National Cancer Institute, Bethesda, MD. NCI-CG-TR-24. Assay performed at Gulf South Research Institute, New Iberia, LA. Report prepared at Tracor Jitco, Rockville, MD under NCI direction. Those responsible for the report at Tracor Jitco were M. Steinberg et al. Reviewed in Document # 000314.

Malathion (technical grade; purity $\geq 95\%$) was administered in the diet to groups of 50 male and 50 female Osborne-Mendel rats (from Battelle Memorial Institute, OH) at time weighted average dosage levels of 4700 or 8150 ppm per group for 80 weeks. Animals were then observed for an additional 29 to 33 weeks. Low dose animals received 8000 ppm in the diet for an initial 14 weeks, which was then adjusted to 4000 ppm for the remaining 66 weeks. High dose animals received 12,000 ppm for an initial 3 weeks, which was then adjusted to 8000 ppm for the remaining 77 weeks. Matched controls consisted of groups of 15 untreated rats of each sex (however, it is noted that matched controls are reported as 2 groups of 10 animals/sex for low dose matched controls and 5 animals/sex for high dose matched controls; the reason for this was that there was an abortive start to the high dose group and when it was reinitiated, the 5 high dose matched controls per sex were added to the original 10 matched controls per sex). Pooled controls consisted of the matched controls combined with 40 untreated male and 40 untreated female rats from similar bioassays of four other test chemicals. These other pooled controls came from bioassays performed at the same laboratory and overlapped the malathion bioassay by at least 1 year. All surviving rats were killed at 108 to 113 weeks.

The Peer Review Committee decided that the analyses that should be of primary importance would be the NTP reevaluation of the original NCI studies (this applies to the three NCI rat studies, two with malathion and one with malaoxon) (these analyses are found in the Huff et al., 1985 article and the E. McConnell memorandum to J. Moore). The Committee felt that the NTP reevaluation provided a more extensive evaluation than the original analysis. Also, there was a consensus of opinion concerning the examined tumors by a panel of expert pathologists.

a. Discussion of Tumor Data

The original NCI report indicated a statistically significant dose-related trend for follicular cell adenomas and carcinomas of the thyroid in female rats. However, there was no significance from a pair-wise comparison. The NCI concluded "there was no clear evidence of the association of the tumor incidence with the administration of malathion."

The NTP reevaluated tissues from these organs (thyroid gland as well as adrenal gland) as potential suggestive targets. They reaffirmed the original NCI conclusion by stating "under the conditions of these studies, there was no evidence of carcinogenicity in male or female Osborne-Mendel rats that received time-weighted average doses of 4700 or 8150 ppm malathion in their diet for 80 weeks." NTP examinations of the major sites of potential targets are shown in Tables 1 and 2. In particular, the NTP reevaluation diagnosed additional follicular cell adenomas in the control and low dose groups that eliminated the positive trend the NCI reported. It was noted by the Peer Review Committee that the NTP did not report hyperplasia incidence although the NTP Summary minutes attached to the McConnell memo states there was no hyperplasia in their C-cell arguments.

Table 1: Malathion Osborne-Mendel Rat Study - Thyroid Findings in NTP Reevaluation

	Sex	C1	C2	Low Dose	High Dose
No. Tissues Examined	M	14	41	35	40
	F	14	41	44	42
C-cell adenoma and carcinoma	M	1 (7.1%)	3 (7.3%)	1 (2.9%)	7 (17.5%)
	F	2 (14.3%)	10 (24.4%)	2 (4.5%)	5 (11.9%)
Follicular Cell Adenoma & Carcinoma	M	2 (14.3%)	8 (19.5%)	9 (25.7%)	12 (30.0%)
	F	0 (0%)	1 (2.4%)	1 (2.3%)	4 (9.5%)

C1 = Matched Controls

C2 = Pooled Controls
(Incidence %)

Table 2: Malathion Osborne-Mendel Rat Study - Pheochromocytoma Findings in NTP Reevaluation

Males	<u>C1</u>	<u>C2</u>	<u>Low Dose</u>	<u>High Dose</u>
Adrenal Gland Pheochromocytoma	0/14 (0%)	2/50 (4%)	0/46 (0%)	5/44 (11%)

C1 = Matched Controls

C2 = Pooled Controls

Number of Lesions/Number of tissues examined (Incidence %)

The Registration Standard for malathion states "the Agency agrees with the NCI/NTP that malathion is not carcinogenic in Osborne-Mendel rats." Subsequent considerations by Toxicology Branch I/Health Effects Division and this Peer Review Committee raise doubt as to how definitive this study is to make a clear conclusion about the carcinogenicity of malathion. The NTP had concluded that under the conditions of this study, there was no evidence of carcinogenicity in male or female Osborne-Mendel rats. However, the Peer Review Committee noted the apparent increases in male C-cell adenomas/carcinomas, of male and female follicular cell adenomas/carcinomas and of male adrenal pheochromocytomas. A detailed independent statistical treatment of the data by statisticians supporting the Peer Review Committee could not be performed as there are not enough data presented (e.g. individual animal data, information about the "pooled" controls) in the NTP reevaluation. This makes it difficult for the Peer Review Committee to make an independent decision based on their own analyses of the data and come to a clear decision regarding the carcinogenicity of malathion in this study.

Although detailed statistical treatment of the NTP data was not able to be performed, it was pointed out that Toxicology Branch I calculated a trend for follicular cell adenomas/carcinomas for females ($p = 0.047$) when compared to matched controls (calculation by B. Dementi and H. Pettigrew (statistician in HED) based on the NTP reevaluated summary numbers). Also, the increasing trend is primarily due to carcinoma incidence (0/14, 0/41, 0/44 and 3/42 for matched controls, pooled controls, low and high dose groups, respectively). The "exact test for trend" was used for cases where relatively few tumors are found and in this instance, provided an increased trend for follicular cell carcinomas compared to pooled controls ($p = 0.034$; B. Dementi and H. Pettigrew calculation; however, $p = 0.071$ compared to matched controls). Carcinoma incidences are viewed with more concern than adenoma incidences.

b. Considerations of Study Adequacy for Assessment of Carcinogenic Potential

The Peer Review Committee questions the adequacy of this study to make definitive conclusions regarding the carcinogenicity of malathion and notes the following: 1) This study was performed before current methods for performing and evaluating an adequate study were in effect. This would introduce uncertainty as to the quality of the study with respect to contemporary guidelines. For example, a significant deviation from the current OPP Subdivision F Pesticide Assessment Guidelines (Series 83-2) is the length of dosing in this study where rats received malathion for 80 weeks instead of a 2 year period. 2) The number of concurrent control animals (15) is very small; this makes comparative analyses difficult when there is not a dramatic difference between tumor incidences. Analysis is also complicated by the use of a concurrent "matched" control group which was divided into two groups of 10 and 5 rats each; these two subgroups exhibited different weight gains. Furthermore, it cannot be concluded with certainty that if a larger concurrent control size had been used, the incidence of spontaneous tumors would rise proportionately. 3) The appropriateness of using "pooled" control animals as "concurrent" controls is unclear. It was in this regard that the historical control incidence from this laboratory was not available to the Peer Review Committee during these deliberations. 4) The NTP states that malathion had no significant effect on survival of male and female Osborne-Mendel rats. The Peer Review Committee noted there were suggestions of a dose-related decrease in survival for both male and female animals near the end of the study. While there were suggested decreases in survival at the end of the study, there were no pair-wise survival disparities between control and dose groups; thus an adjusted tumor analysis is not necessary.

2. Malathion - Fischer 344 Rat Dietary Feeding Carcinogenicity Study

Reference: National Cancer Institute. 1979. Bioassay of malathion for possible carcinogenicity, CAS No. 121-75-5. Technical Report Series, No. 192, National Cancer Institute, Bethesda, MD. NCI-CG-TR-192. Assay performed at Gulf South Research Institute, New Iberia, LA. Report prepared at Tracor Jitco, Rockville, MD under NCI direction. Those responsible for the report at Tracor Jitco were C.R. Angel et al. Reviewed in Document # 000314.

Malathion (manufacturer's assay; purity 95%) was administered in the diet to groups of 49 to 50 Fischer 344 rats of each sex (from NCI Frederick Cancer Research Center, MD) at doses of 2000 or 4000 ppm per group for 103 weeks. Animals were then observed for an additional 2 or 3 weeks. Matched controls consisted of 50 untreated rats per sex. All surviving rats were killed at 105 to 106 weeks.

a. Discussion of Tumor Data

The original NCI report stated "malathion was not carcinogenic in male or female rats, but the females may not have received a maximum tolerated dose." The NCI acknowledged that the increase in adrenal gland pheochromocytomas in low dose males was statistically significant by pair-wise comparison, but did not consider this to be associated with the administration of malathion. This conclusion was based on the lack of an effect at the high dose and the lack of a dose response effect.

The NTP reevaluated tissues from the male adrenal gland. They reaffirmed the original NCI conclusion by stating "under the conditions of these studies, there was no evidence of carcinogenicity in male or female Fischer 344 rats that were provided diets containing 2000 or 4000 ppm malathion for 103 weeks." However, the NTP suggested that two neoplasms appeared to be increased in the low dose males: pheochromocytoma of the adrenal gland (Table 3) and leukemia (Table 4; note the NCI did not comment on this lesion). However, these marginal increases were only significant by life-table analyses. The NTP suggested that life-table analyses are appropriate if the lesion is the cause of death. The NTP judges that the early deaths seen in this study (discussed below) are due to chemical toxicity. However, the increases in these two tumor types were not significant by incidental tumor tests or pair-wise tests. The NTP suggested that the reduced survival in the dosed groups made the overall interpretation of the data difficult.

Table 3: Malathion Fischer 344 Rat Study - Pheochromocytoma Findings in NTP Reevaluation

Males	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Adrenal Gland	5/49 (10%)	10/48 (21%)	6/46 (13%)
Pheochromocytoma			
Number of Lesions/Number of tissues examined (Incidence %)			

Table 4: Malathion Fischer 344 Rat Study - Leukemia Findings in NTP Reevaluation

Males	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic	13/50 (26%)	20/50 (40%)	8/49 (16%)
System - Leukemia			
Number of Lesions/Number of tissues examined (Incidence %)			

The Registration Standard for malathion states "the Agency agrees with the conclusions of the NCI/NTP, but notes that the dose levels employed in this study were approximately one-half of those employed in the NCI Osborne-Mendel rat study, and that therefore it is unlikely the maximum tolerated dose was reached in females." Subsequent considerations by Toxicology Branch I/Health Effects Division and this Peer Review Committee raise doubt as to how definitive this study is to make a clear conclusion about the carcinogenicity of malathion. The NTP had concluded that under the conditions of this study, there was no evidence of carcinogenicity in male or female Fischer 344 rats. However, the Peer Review Committee noted the apparent increases in male adrenal pheochromocytomas and male leukemia at the low dose. An independent statistical treatment of the data by statisticians supporting the Peer Review Committee could not be performed as there are not enough data presented (e.g. individual animal data) in the NTP reevaluation. The large decrease in survival of exposed males confounds the interpretation of potential tumor induction. This makes it difficult for the Peer Review Committee to make an independent decision based on their own analyses of the data and come to a clear decision regarding the carcinogenicity of malathion in this study.

b. Consideration of Study Adequacy for Assessment of Carcinogenic Potential

Other considerations about the adequacy of this study were made by the Committee: 1) While this study employed lower doses than the Osborne-Mendel rat study, there was a major problem with mortality in the Fischer 344 rats, especially in the males. Survival at 103 weeks for males was 54%, 28% and 0% for control, low- and high-dose groups, respectively. For females, the comparable figures were 64%, 52% and 50%. In males, it was noted there was not a great disparity in survival figures among groups at 90 weeks, so increased mortality rates appeared after this time. The large drop in survival in males confounds the observations found at the high dose where apparently less animals were at risk for tumor induction. It is not clear how this may have impacted upon a possible dose-response association. Despite the small decrease in survival for females, it was suggested that the top dose may not be high enough for a definitive assessment of carcinogenic potential. 2) The concurrent control incidence for pheochromocytomas in males tabulated by the NTP was discussed. In the NTP reevaluation, this incidence is reported to be 10% (5/49 animals). The original NCI review reported the incidence to be 4% (2/49 animals; three less than the NTP reevaluation). This latter value appears more in line with the historical control incidence from the testing laboratory of 3% (8/275 animals) among males. It is not known what the range of control values from separate studies in the historical database is from the testing laboratory. Therefore, the issue of the NTP concurrent control incidence and

what it means to the statistical evaluation of the tumors observed in this study is not resolved. 3) Like the Osborne-Mendel rat study, this study was performed before the current OPP Subdivision F Pesticide Assessment Guidelines (Series 83-2) were in place. This would introduce uncertainty as to the quality of the study with respect to contemporary guidelines. However, unlike the Osborne-Mendel rat study, this study employed a more appropriate number of concurrent control animals and dosing was performed over a 2 year period.

c. Non-Neoplastic Findings

Several significant non-neoplastic findings were noted. Stomach inflammation and ulceration were clearly increased in a dose-related fashion among males. Also, there were increased incidences of fatty metamorphosis and focal cellular changes of the liver for females and chronic inflammatory change of the kidney in females. These non-neoplastic findings help provide support for the Agency's decision to require a full 2 year chronic toxicity study in the Fischer 344 rat as detailed in the Registration Standard.

3. Malathion - Sprague-Dawley Rat Dietary Feeding Carcinogenicity Study

Reference: Rucci, G., P.J. Becci and R.A. Parent. May 13, 1980. The evaluation of the chronic toxicity effects of Cythion administered in the diet to Sprague-Dawley rats for 24 consecutive months. Unpublished study (No. 5436) prepared by Food and Drug Research Laboratories, Inc., Waverly, NY for Agricultural Division, American Cyanamid Co., Princeton, NJ. Reviewed in Document #: 002504, 004208).

Malathion (technical Cythion; purity 92.1%) was administered in the diet to groups of 50 male and 50 female Sprague-Dawley rats (from Blue Spruce Farms, NY) at doses of 100, 1000 or 5000 ppm per group for 24 months. Matched controls consisted of 50 untreated rats per sex. Surviving animals were killed at the end of the 24 month period (104 weeks).

The malathion Registration Standard states "this study was determined by the Agency to be unacceptable for use as either a chronic rat toxicity study or as a rat oncogenicity (sic) study. An independent reevaluation of the microscopic slides from this study is required in order to determine the acceptability of this study." However, it is not clear that an independent review will resolve all the problems associated with this study (detailed below) and elevate it to an acceptable study.

a. Consideration of Study Adequacy for Assessment of Carcinogenic Potential

This study was determined by the Peer Review Committee to be insufficient to provide definitive evidence on the carcinogenicity of malathion. A final review of this study in a Data Evaluation Report prepared by R.B. Jaeger (July 17, 1987) concluded this study should be classified as invalid. Many reasons were provided for the invalid classification, including: the summary tables do not distinguish between animals killed at term and animals found dead, killed moribund or accidental deaths; pathology slides were not read "blind"; rather each pathologist had prior knowledge of the dose level administered; there is no indication of the numerical rating for the degree or severity of change observed by each pathologist; there were several pathologists involved which raises substantial concern for "consistency" and "uniformity", especially in light of several apparent discrepancies noted in the findings; animals which died, killed moribund or accidental deaths were not examined in a manner to preclude autolysis of tissue; animals in all groups suffered from substantial degrees of several illnesses, raising a question about good animal husbandry for this study; the substantial amount of geriatric changes in all groups makes it extremely difficult to separate or identify normal ageing processes from compound-related effects; kidney, pituitary, adrenal and thyroid weights were selectively screened and eliminated from the organ weight and organ-to-body weight comparisons if they were above or below pre-selected values; sufficient information for examining biochemical and clinical effects in a chronic bioassay were not obtained; and, use of chloroform to euthanize animals at termination of the study is not presently a common practice as it is a suspect carcinogen and may induce potential adverse effects on its own. These points serve to illustrate the substantial faults in the study design, conduct and reporting of this study.

b. Discussion of Tumor Data

Even though this study was found to be invalid, a statistical analysis was performed and some effects were noted (memorandum C.J. Nelson, July 21, 1987; it is realized that this is an analysis on unverified summary data and has not undergone secondary review). Uterus polyps in females had no significant trend, but both high and low dose groups were significantly different from controls by pair-wise comparison. There was a significant trend, but no pair-wise comparison difference for thyroid parafollicular cell (C-cell) malignant tumors in female rats. It was concluded by the Peer Review Committee however that there should not be much weight put upon these findings, although it was noted that C-cell tumors had been observed in the Osborne-Mendel rat study.

c. Non-Neoplastic Findings

Many chronic effects were noted in this study, some even at the low dose of 100 ppm. Statistical analysis (memorandum C.J. Nelson, July 21, 1987) revealed several significant effects which included: swollen liver and kidney glomerulosclerosis, prostate calcification, liver sinusoidal dilation, lymph node reticuloendothelial hyperplasia, pituitary cyst, and heart inflammation in male rats; kidney tubular casts, spleen extramedullary hematopoiesis, thymus cyst, uterus pyometra, kidney tubular dilation, and pancreas duct dilation in female rats. Although this study is unacceptable for a chronic toxicity study, these effects suggest concern for chronic non-neoplastic adverse effects induced by malathion.

4. Malathion - B6C3F1 Mouse Dietary Feeding Carcinogenicity Study

Reference: National Cancer Institute. 1978. Bioassay of malathion for possible carcinogenicity, CAS No. 121-75-5. Technical Report Series, No. 24, National Cancer Institute, Bethesda, MD. NCI-CG-TR-24. Assay performed at Gulf South Research Institute, New Iberia, LA. Report prepared at Tracor Jitco, Rockville, MD under NCI direction. Those responsible for the report at Tracor Jitco were M. Steinberg et al. Reviewed in Document # 000314.

Malathion (technical grade; purity $\geq 95\%$) was administered in the diet to groups of 50 male and 50 female B6C3F1 mice (from Charles River Breeding Laboratories, MA) at doses of 8000 or 16,000 ppm per group for 80 weeks. Animals were then observed for an additional 14 or 15 weeks. Matched controls consisted of groups of 10 untreated mice of each sex. Pooled controls consisted of the matched controls combined with 40 untreated male and 40 untreated female mice from similar bioassays of four other test chemicals. These other pooled controls came from bioassays performed at the same laboratory and overlapped the malathion bioassay by at least 1 year. All surviving mice were killed at 94 to 95 weeks.

a. Discussion of Tumor Data

The NCI concluded that under the conditions of this study, there was "no clear evidence" of an association between malathion administration and tumor incidence. The NCI report noted a possible increased incidence of hepatocellular carcinoma in male mice (see Table 5). Statistical treatment showed a dose-related trend ($p = 0.019$) when neoplastic nodules and hepatocellular carcinoma were combined and compared to pooled controls. The direct comparison between the high-dose group and the pooled control group for combined nodules and carcinoma revealed a significant difference ($p = 0.031$ Fisher's Exact Test); however, the NCI employed as its criterion of significance $p = 0.025$, based

on Bonferroni adjustments, and therefore did not consider this a positive finding. The NTP did not reexamine this study.

Table 5: Malathion B6C3F1 Mouse Study - Liver Findings from NCI Evaluation

Males	<u>C1</u>	<u>C2</u>	<u>Low Dose</u>	<u>High Dose</u>
Hepatocellular Carcinoma	2/10 (20%)	5/49 (10.2%)	7/48 (14.6%)	11/49 (22.5%)
Neoplastic Nodules & Hepatocellular Carcinoma	-----	8/49 (16.3%)	7/48 (14.6%)	17/49 (34.7%)

C1 = Matched Controls

C2 = Pooled Controls

Number of Lesions/Number of tissues examined (Incidence %)

The Registration Standard states "because of study design flaws and the questionable liver findings (i.e. dose-related trend ($p = 0.019$) and increased incidence of hepatocellular carcinomas at the high dose ($p = 0.031$)), another study in mice is required." Further considerations by Toxicology Branch I/Health Effects Division and this Peer Review Committee also raise doubt as to how definitive this study is to make a clear conclusion about the carcinogenicity of malathion. The NCI did not consider the pairwise comparison ($p = 0.031$) significant based on Bonferroni adjustments. It was further noted that the current NTP practice for evaluating common tumors from data representative of the NTP/NCI historic database that Haseman's rule of thumb (Haseman et al., Fund Appl Toxicol 7: 573-584, 1986) would apply where p values of 0.01 or less denotes significance. However, from the NCI evaluation, there are not enough data presented (e.g. individual animal data, information about the "pooled" controls) to allow an independent statistical treatment of the data by statisticians supporting the Peer Review Committee. This makes it difficult for the Peer Review Committee to make an independent decision based on their own analyses of the data. Therefore, it is not entirely clear that the suggestive evidence of male hepatocellular carcinoma and combined neoplastic nodules/hepatocellular carcinoma can be totally dismissed. Furthermore, it was noted that a large proportion of the increased tumor numbers was due to an increase in carcinoma. Although detailed statistical treatment of the NCI data was not able to be performed, it was pointed out that Toxicology Branch I calculated a trend for hepatocellular carcinomas ($p = 0.046$; calculation by B. Dementi and H. Pettigrew (statistician in HED) based on the NCI summary numbers). Carcinoma

incidences are viewed with more concern than adenoma incidences.

b. Considerations of Study Adequacy for Assessment of Carcinogenic Potential

The Peer Review Committee made the following observations about the adequacy of this study to make definitive conclusions regarding the carcinogenicity of malathion: 1) The number of concurrent control animals (10) is a very small group; this makes comparative analyses difficult when there is not a dramatic difference between tumor incidences. It cannot be concluded with certainty that if a larger concurrent control size had been used, the incidence of spontaneous tumors would rise proportionately. 2) The appropriateness of using "pooled" control animals as "concurrent" controls is unclear. 3) It was noted that the historical control incidence data for hepatocellular carcinoma in this strain of mouse often is higher than that observed in the high-dose group seen in this study. 4) The Registrant points out that the dose levels employed in this study (8000 and 16,000 ppm) exceed the OPP accepted upper limit dose of 1.0 g/kg/day in mouse carcinogenicity studies. 5) The NCI report lists a number of signs of disease appearing "with increasing frequency in dosed animals", especially at weeks 72 and beyond to the end of the study. This raises questions about the general health of animals during a crucial period of the study. 6) This study was performed before the current OPP Subdivision F Pesticide Assessment Guidelines (Series 83-2) were in place. This would introduce uncertainty as to the quality of the study with respect to contemporary guidelines.

Since there were many uncertainties about the conduct of this study and the questionable liver findings, the Peer Review Committee endorsed the requirement for an additional mouse carcinogenicity study with malathion to help clarify any possible carcinogenic potential by malathion.

5. Malaoxon - Fischer 344 Rat Dietary Feeding Carcinogenicity Study

Reference: National Cancer Institute. 1979. Bioassay of malaoxon for possible carcinogenicity, CAS No. 1634-88-2. Technical Report Series, No. 135, National Cancer Institute, Bethesda, MD. NCI-CG-TR-135. Assay performed at Gulf South Research Institute, New Iberia, LA. Report prepared at Tracor Jitco, Rockville, MD under NCI direction. Those responsible for the report at Tracor Jitco were C.R. Angel et al. Reviewed in Document # 000314.

Malaoxon (synthesized by testing laboratory, purity >95%) was administered in the diet to groups of 50 male and 50 female Fischer 344 rats (from NCI Frederick Cancer Research Center, MD) at doses

of 500 or 1000 ppm per group for 103 weeks. Animals were then observed for up to an additional 2 weeks. Matched controls consisted of 50 untreated rats per sex. All surviving rats were killed at 103 to 105 weeks.

a. Discussion of Tumor Data

The original NCI report concluded that under the conditions of this study, malaoxon was not carcinogenic in Fischer 344 rats. The review did note a possible increase in thyroid C-cell adenomas or carcinomas in female rats at the high dose. However, this positive finding for C-cell tumors was questioned by reference to "historical" control data. The review states "the historical record of this laboratory shows an incidence of female F344 rats with C-cell adenomas or carcinomas of 16/223 (7%), compared with 0/50 in the control group, 1/49 (2%) in the low-dose group and 5/47 (11%) in the high-dose group of this study. This indicates that the incidence of C-cell tumors of the thyroid in female rats of the present study is comparable to that usually seen in control animals."

The NCI report also revealed an increased incidence of benign mammary gland tumors in low-dose females ($p = 0.026$). However, this increase was not considered to be significant as the NCI employed as its criteria of significance $p = 0.025$, based on Bonferroni adjustments, and therefore did not consider this a positive finding. The original NCI report also noted an increase in the incidence of adrenal gland pheochromocytoma in males, but reported these increases were not statistically significant.

The NTP reevaluated tissues from these organs (thyroid gland, adrenal gland) as potential suggestive targets. The NTP reevaluation revealed one difference from the original NCI review. The NTP concluded that there was equivocal evidence of carcinogenicity for male and female F344 rats based on findings for C-cell neoplasms of the thyroid gland (Huff et al., 1985). NTP examinations of the major sites of potential targets are shown in Table 6. In particular, the NTP reevaluation resulted in an increase in incidence of C-cell tumors in females that was significant at the high-dose ($p = 0.045$, pair-wise comparison) and yielded a dose-related trend. For males, the NTP reported a positive finding for C-cell adenomas and carcinomas in the high-dose group ($p = 0.035$, pair-wise comparison) and a positive trend. The NTP reevaluation also showed an increase in the incidence of mammary gland adenomas in low-dose females, but this increase was dismissed as related to malaoxon administration as the increase was not seen at the high dose and the incidence in the concurrent controls was unusually low. The subsequent NTP reevaluation resulted in a considerable revision in the incidence of pheochromocytoma from that in the original NCI report; however, the NTP did not indicate any statistically significant findings for

this tumor.

The NTP provided a detailed description of their reasoning for considering the equivocal evidence for C-cell neoplasms of the thyroid gland (Huff et al., 1985). Arguments for an associative effect by malaoxon, from the publication, are: (i) dose-response trends in both sexes, (ii) the incidences in the high-dose groups were increased, albeit marginally, in comparison to concurrent controls, (iii) the incidences exceed the historical rates observed in this species (male F344 rats, 196/2230, 8.8%; female F344 rats, 190/2265, 8.4%), and (iv) six carcinomas were found in the high-dose groups, compared with one in the controls. The arguments against this being a malaoxon related response are: (i) no corresponding increases were seen for hyperplasia (see Table 6 below), (ii) the neoplasms were microscopic in size and morphologically identical to naturally occurring tumors, (iii) no supporting effects were observed in Study II of malathion in F344 rats or in the Study I of malathion in Osborne-Mendel rats, both at higher doses, and (iv) the incidence in the concurrent control group was somewhat lower than the rates observed in Study II of malathion and the mean historic control.

Table 6: Malaoxon Fischer 344 Rat Study - Findings in
NTP Reevaluation

	Sex	Control	Low Dose	High Dose
Thyroid C-cell hyperplasia	M	8/49 (16%)	11/45 (24%)	8/49 (16%)
	F	24/48 (50%)	24/48 (50%)	25/48 (52%)
Thyroid C-cell adenoma & carcinoma	M	3/49 (6%)	3/45 (7%)	10/49 (20%) *
	F	4/48 (8%)	7/48 (15%)	11/48 (23%) *
Adrenal Pheochromocytoma	M	5/50 (10%)	6/50 (12%)	10/49 (20.4%)
Mammary gland adenoma	F	2/50 (4%)	9/50 (18%)	1/50 (2%)
Hematopoietic system lymphoma	M	0/50 (0%)	0/50 (0%)	4/50 (8%)

Number of Lesions/Number of tissues examined (Incidence %)

* may be 12/48 (25%) for females

The Registration Standard for malathion requires that the Registrant perform an additional Fischer 344 rat study using malaoxon. The stated purpose of this additional study is to

clarify the carcinogenic potential of malaoxon and provide additional needed data on the effects of malaoxon on cholinesterase inhibition. Further considerations by Toxicology Branch I/Health Effects Division and this Peer Review Committee raise doubt as to how definitive this study is to make a clear conclusion about the carcinogenicity of malaoxon. Again, as in the Osborne-Mendel rat study, the NTP does not provide detailed data from which to perform independent statistical analyses. Therefore, it is not entirely clear that the suggestive evidence of male adrenal gland pheochromocytomas and of female mammary gland adenomas at the low dose can be totally dismissed.

The Peer Review Committee agrees with the NTP language regarding the equivocal evidence for the C-cell neoplasms of the thyroid gland; i.e. "equivocal evidence of carcinogenicity is demonstrated by studies that are interpreted as showing a chemically-related marginal increase of neoplasms." The Peer Review Committee made several comments on the detailed reasoning the NTP provided on the equivocal classification. 1) While the incidences of C-cell neoplasms are above the mean historical values provided by the NTP, it is not clear what the range of values were from the individual studies that made up the historical database. This may have some bearing on the significance of the increased thyroid findings. 2) It was noted that the thyroid C-cell rate for hyperplasia was not significantly elevated over control. 3) It was considered that the elevated number of carcinomas observed was a significant contribution to the possible chemical induced effect by malaoxon. For example, there was a positive trend for C-cell carcinomas alone for females ($p = 0.015$) although the pair-wise comparison was $p = 0.059$. 4) As regards to the possible low concurrent control group incidence, it was noted that the NTP incidence was similar to the original NCI incidence. 5) There was question as to whether it can be definitively concluded that there were no supporting effects seen in the two malathion rat carcinogenicity studies.

It was also noted in the NTP reevaluation (but not discussed by the NTP), there was an evident increase in the incidence of lymphoma (hematopoietic system) among high dose males. Although detailed statistical treatment of the NTP data was not able to be performed, it was pointed out that Toxicology Branch I calculated a trend for lymphoma ($p = 0.006$; calculation by B. Dementi and H. Pettigrew (statistician in HED) based on the NTP reevaluated summary numbers). The pair-wise comparison however was $p = 0.059$. The "exact test for trend" was used for cases where relatively few tumors are found and in this instance, provided an increased trend for lymphoma ($p = 0.0114$; B. Dementi and H. Pettigrew calculation). It was noted that in some cases, lymphoma and leukemia are combined by the NTP. Leukemia was suggested in the Fischer 344 rat malathion study.

Therefore, due to the uncertainty of the total findings in this malaoxon study, the Peer Review Committee reaffirms the Registration Standard requirement for an additional rat carcinogenicity study using malaoxon.

b. Consideration of Study Adequacy for Assessment of Carcinogenic Potential

Another consideration by the Peer Review Committee and Toxicology Branch I provides support for requiring an additional rat study with malaoxon. The percent survival at week 90 of the study for males and females, respectively, was 80% and 82% for controls, 82% and 90% for the low dose group, and 64% and 80% for the high dose group. For the male animals, the Peer Review Committee noted there were suggestions of a dose-related increase in mortality. However, there were no pair-wise survival disparities between control and dose groups; thus an adjusted tumor analysis is not suggested. Furthermore, while it is not clear if the NTP took the higher mortality into account in their deliberations, the NTP mentioned in their reevaluation that sufficient numbers of rats of each sex were at risk for the development of late appearing tumors.

c. Non-Neoplastic Findings

The NTP reports that in this study forestomach ulcers were observed at increased incidences in male and female rats (males: 3/47, 6%, control; 7/48, 14%, low dose; 9/48, 18%, high dose; and, females: 0/49, 0%, control; 1/48, 2%, low dose; 3/48, 6%, high dose). This is similar to the findings evaluated by the NTP in the malathion Fischer 344 rat study.

6. Malaoxon - B6C3F1 Mouse Dietary Feeding Carcinogenicity Study

Reference: National Cancer Institute. 1979. Bioassay of malaoxon for possible carcinogenicity, CAS No. 1634-88-2. Technical Report Series, No. 135, National Cancer Institute, Bethesda, MD. NCI-CG-TR-135. Assay performed at Gulf South Research Institute, New Iberia, LA. Report prepared at Tracor Jitco, Rockville, MD under NCI direction. Those responsible for the report at Tracor Jitco were C.R. Angel et al. Reviewed in Document # 000314.

Malaoxon (synthesized by testing laboratory, purity >95%) was administered in the diet to groups of 50 male and 50 female B6C3F1 mice (from NCI Frederick Cancer Research Center, MD) at doses of 500 or 1000 ppm per group for 103 weeks. Animals were then observed for up to an additional 2 weeks. Matched controls consisted of 50 untreated mice per sex. All surviving mice were killed at 103 to 105 weeks.

The NCI report concluded that under the conditions of this study, malaoxon was not carcinogenic in the B6C3F1 mouse. The OPP review of this study concurred with the NCI in this opinion and the malathion Registration Standard does not call for additional testing of malaoxon in the mouse.

E. Additional Toxicology Data on Malathion:

1. Acute Toxicity

Technical malathion is mildly toxic on an acute oral (Category III), dermal (Category III) and inhalation (Category III) basis. Technical malathion is only mildly irritating to the eye of rabbit (Category III) and slightly irritating after dermal exposure to rabbit (Category IV). Technical malathion is nonsensitizing by dermal application. No data are available on the acute delayed neurotoxicity of malathion in the hen and, since malathion is an organophosphate, this study is required.

2. Metabolism

According to the Malathion Registration Standard issued in February, 1988, there are data gaps in the chronic toxicology data base which includes a data gap for metabolism studies. The OPP has just recently received a study concerning malathion metabolism and it is currently undergoing review. It is considered that malaoxon is a metabolite of malathion. However, it is not clear how much malathion is metabolized to malaoxon. Since malaoxon is considered a metabolite of malathion, and may be responsible for some or all malathion toxic effects, malaoxon was also examined for carcinogenicity in long term bioassays.

3. Mutagenicity

According to the Malathion Registration Standard issued in February, 1988, there are no data available on the mutagenic potential of malathion. Studies are required in all of the following mutagenicity test areas: gene mutation, structural chromosomal aberrations, and other genotoxic effects. While there are no acceptable studies submitted to the OPP, there are many open literature articles concerning mutagenicity testing with malathion and malaoxon. Tables 7 and 8 present a listing of many of these tests (this is not prepared as an exhaustive or critical review).

Table 7. Open Literature Mutagenicity Studies on Malathion

Gene Mutation Category

Salmonella assay

Haworth et al., Environ Mutagen 5 (Suppl 1): 3-142, 1983

Moriya et al., Mutat Res 116: 185-216, 1983

Waters et al., Basic Life Sci 21: 275-326, 1982

Other references

Results: all Negative

E. coli reverse mutation (WP2; WP2 uvr A)Brusick et al., Mutat Res 76: 169-190, 1980Waters et al., Basic Life Sci 21: 275-326, 1982Moriya et al., Mutat Res 116: 185-216, 1983

Results: all Negative

Mouse lymphoma assay

NTP, 1988 Annual Plan

Result: Equivocal

Drosophila sex-linked recessive lethal assay

Waters et al., Basic Life Sci 21: 275-326, 1982Velazquez et al., Environ Mutagen 9: 343-348, 1987

Results: all Negative

Structural Chromosomal Aberrations Category

In vitro mammalian cell aberrations

Galloway et al., Environ Mol Mutagen 10 (Suppl 10): 1-175, 1987

Result: CHO cells, Negative w/o activation, Positive w/act.

Ishidate et al., Mutat Res 195: 151-213, 1988Results: CHL cells, Positive \pm activation

human lymphocytes, Positive w/o activation

human hematopoietic B411-4 cells, Negative w/o act.

In vivo mammalian aberrations - bone marrow

Dulout et al., Mutat Res 122: 163-167, 1983

Result: Positive, one i.p. dose Balb/c mouse

Degraeve and Moustschen, Environ Res 34: 170-174, 1984

Result: Negative, one i.p. dose Q strain mouse

Degraeve et al., Arch Toxicol 56: 66-67, 1984

Result: Negative, 7 weeks drinking water, a low dose (8 ppm)

Dzwonkowska and Hubner, Arch Toxicol 58: 152-156, 1986

Result: weak Positive, one i.p. dose Syrian hamster

Salvadori et al., Mutat Res 204: 283-287, 1988Result: one dose, Negative; multiple doses (5 days/2 weeks),
Positive; Swiss Webster mice

Mouse micronucleus

Dulout et al., Mutat Res 105: 413-416, 1982

Result: Positive, cutaneous route; weak Positive, i.p. route

In vivo human - acute malathion intoxication

van Bao et al., Humangenetik 24: 33-57, 1974

Result: increase in breaks in lymphocytes

In vivo mammalian aberrations - germ cells

Degraeve and Moustschen, Environ Res 34: 170-174, 1984

Result: Negative, spermatogonia, one i.p. dose Q strain mouse

Degraeve et al., Arch Toxicol 56: 66-67, 1984
 Result: Negative, spermatogonia and primary spermatocytes, 7 weeks - drinking water, 8 ppm, Q strain mouse
 Salvadori et al., Mutat Res 204: 283-287, 1988
 Result: one dose, primary spermatocytes, Negative
 multiple doses, primary spermatocytes, Positive
 Swiss Webster mice

Dominant lethal assay - mouse
 3 reported Negative studies, but problems with each study

Note: Krause et al., Bull Environ Contam Toxicol 15: 458-462, 1976
 Result: found slight damage to testicular tissues, but recovered (indicates malathion can reach germ cell area)

Other Genotoxic Effects Category

In vitro mammalian cells - SCE

Galloway et al., Environ Mol Mutagen 10 (Suppl 10): 1-175, 1987
 Result: Positive \pm activation, CHO cells
 Nicholas et al., Mutat Res 67: 167-172, 1979
 Result: Positive w/o activation, human fetal lung fibroblasts
 Nishio and Uyeki, J Toxicol Environ Health 8: 939-946, 1981
 Result: Positive w/o activation, CHO cells
 Chen et al., Mutat Res 88: 307-316, 1981
 Result: weak, but dose response Positive w/o act., V79 cells
 Chen et al., Environ Mutagen 4: 621-624, 1982
 Result: weak, but dose response Positive with act., V79 cells
 Sobti et al., Mutat Res 102: 89-102, 1982
 Result: Positive \pm activation, human lymphoid cells (LAZ-007)

UDS in WI-38 cells

Waters et al., Basic Life Sci 21: 275-326, 1982
 Result: Negative

Mitotic recombination in Saccharomyces

Waters et al., Basic Life Sci 21: 275-326, 1982
 Result: Negative

Differential toxicity in DNA repair deficient strains of E. coli and B. subtilis

Waters et al., Basic Life Sci 21: 275-326, 1982
 Result: Negative

Other:

Griffin and Hill, Mutat Res 52: 161-169, 1978
 Result: induced in vitro breakage of plasmid DNA at a slow rate, but significantly greater than control rate

Table 8. Open Literature Mutagenicity Studies on Malaoxon

Gene Mutation Category

Salmonella assay

Zeiger et al., Environ Molec Mutagen 11 (Suppl 12): 1-158, 1988
 Result: Negative

Mouse lymphoma assay

Tennant et al., Science 236: 933-941, 1987
 Result: Positive without activation

Structural Chromosomal Aberrations Category

Aberrations/CHO cells

Ivett et al., Environ Molec Mutagen 14: 165-187, 1989
 Result: Negative

Other Genotoxic Effects Category

SCE/CHO cells

Ivett et al., Environ Molec Mutagen 14: 165-187, 1989
 Result: Positive + activation, but weak with activation
 Nishio and Uyeki, J Toxicol Environ Health 8: 939-946, 1981
 Results: Positive without activation (slightly greater than malathion)

These mutagenicity data suggest malathion has genetic activity. While malathion is generally negative in all point mutation assays, it is positive in all the available in vitro sister chromatid exchange assays. There are both positive and negative findings for structural chromosomal alterations. While there are negative aberration studies for malathion, there are sufficient positive findings in both in vitro and in vivo cytogenetic assays and in both somatic and germ cells to warrant a mutagenicity concern. This information provides support for a possible genetic component in the weight of evidence consideration for carcinogenicity. The limited amount of available malaoxon mutagenicity data appear similar to the malathion data.

4. Developmental and Reproductive Effects

A developmental study was performed with New Zealand rabbits. Twenty female rabbits per dose group were exposed via gastric intubation to single daily doses of vehicle (corn oil) or malathion on days 6 to 18 gestation. Dose levels used were 25, 50 and 100 mg/kg body weight per exposure. Animals were observed between days 0 to 20 of gestation. No adverse developmental effects were seen. Due to decreased dam body weight gain at 50 mg/kg/day and increases

in mean percent of resorptions at the top two dose groups, the developmental No Observable Effect Level (NOEL) is 25 mg/kg/day and the maternal NOEL is also 25 mg/kg/day.

The Registration Standard for malathion states that a rat developmental toxicity study is required to support registration of products containing malathion. This study has just recently been submitted and is currently undergoing review. A reproduction study in the rat is also required to be performed and this study is currently in progress.

5. Structure-Activity Correlations

There was not a great deal of discussion regarding possible structure-activity correlations with malathion. It appears that as a general class organophosphates are not consistent in their actions, as evidenced by differences in toxicity, metabolism, distribution, etc. This may be due to the differences in chemical groups attached to the phosphate portion of the organophosphates. The variety of these groups may provide an explanation for the inconsistency in organophosphate SAR. However, it was noted that malaoxon is a metabolite and structural analogue of malathion. This suggests that malaoxon is an appropriate analogue and important metabolite for comparison to malathion. Several of the suggestive findings in the malathion rat carcinogenicity studies are apparent in the malaoxon rat carcinogenicity study. These included lesions in the thyroid and adrenal glands. Furthermore, some non-neoplastic findings were comparable, especially the occurrence of stomach ulceration. Finally, the genetic toxicity data appear to be similar between malathion and malaoxon, at least based on the limited amount of data available for malaoxon.

4) The mutagenicity data suggest that malathion has genetic activity. This information provides some support for a possible genetic component in the weight of evidence consideration for carcinogenicity. The limited amount of available malaoxon mutagenicity data appear similar to the malathion data.

5) The NTP has indicated in its memorandum to J. Moore (from E. McConnell) that the NTP is considering a further study of malathion using current "state-of-the-art" methods. There has been no further information on this intention. Furthermore, the NTP's Board of Scientific Counselors has recommended that there is need for a state of art carcinogenesis study for malathion (NTP Fiscal Year 1986 Annual Plan, NTP Publication No. NTP-86-086). This indicates that although they have no reason to believe malathion is carcinogenic, there is a perceived need for a state-of-the-art carcinogenicity study for malathion.

G. Classification of Carcinogenic Potential:

Criteria contained in the EPA Guidelines [FR51: 33992-34003, 1986] for classifying a carcinogen were considered.

The Peer Review Committee agreed to classify malathion as a Group D Carcinogen; that is, malathion is not classifiable as to human carcinogenicity. The Peer Review Committee decision was based on the inadequacy of the available studies to make definitive determinations on the carcinogenicity of malathion and malaoxon. The Committee agreed with the NTP reanalysis that there was no clear evidence of carcinogenicity due to malathion or malaoxon administration in most of these studies (the NTP concluded equivocal evidence in the malaoxon rat study). This is also consistent with past Agency positions. However, the Committee felt there were many issues regarding the adequacy of each study from which a firm conclusion on the carcinogenic potential of malathion could not be made.

In addition, while there may have been doubts about the significance of each tumor type in each of the individual studies, there was the suggestive appearance of similar tumors (e.g. C-cell neoplasms of the thyroid gland and pheochromocytomas of the adrenal gland) and of multiple tumors in more than one study. Also, there was some evidence from mutagenicity studies that a genetic component for malathion and malaoxon is possible. These points provided weight to the evidence of possible carcinogenic effects that could not be totally dismissed.

Because of the unresolved questions about the adequacy of the existing studies vis-a-vis current standards and the potential effects noted in these existing studies, additional studies need to be performed to address these concerns. The Committee reaffirmed the requirement of the Malathion Registration Standard that requires the Registrant to perform an additional mouse carcinogenicity study with malathion. The Committee also determined that the Registration Standard recommendation to perform a carcinogenicity study in combination with a rat chronic study on malathion be made into a requirement. It is believed these studies using current standards are necessary for a more adequate assessment of malathion.

The Committee also reaffirmed the requirement to perform an additional rat carcinogenicity study with malaoxon. Since malaoxon was considered the metabolite of malathion that produces much of the effects of malathion, it was felt important to properly assess the carcinogenicity of malaoxon. Also, in several instances (e.g. Daminozide/UDMH, EBDCs/ETU), the quantitative risk assessment has been based on the metabolite where tumorigenicity may be more apparent at lower doses with the metabolite when it is the tumor inducing agent. For these reasons, a well conducted study on malathion's metabolite, malaoxon, would be required.