2-2-95

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review for MGK-264.

TOX CHEM No.: 613
PC No.: 057001

FROM: John Doherty 2/1/95
Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO: Esther Rinde, Ph.D.
Carcinogenicity Peer Review Manager
Science Analysis Branch
Health Effects Division (7509C)

THROUGH: Marion Copley, DVM, Section Head Marion Copley 2/1/95
Section IV, Toxicology Branch I
Health Effects Division (7509C)

and

Karl Baetcke, Ph.D.
Chief, Toxicology Branch I
Health Effects Division (7509C) KB 2/2/95

Attached are parts C, D, E and F for incorporation into the Peer Review Document for MGK-264.

The carcinogenicity issues of concern are:

-liver tumors in male and female mice.
-thyroid tumors in male rats.

-adequacy of dosing for both studies for both sexes.

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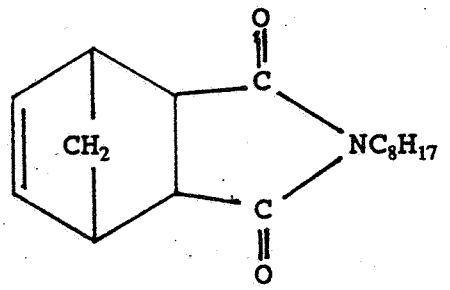
A. and B. Parts A and B are not included in this document (to be prepared by the Peer Review Committee).

C. Background Information:

MGK-264 is an insecticide synergist that disrupts the degradation of pesticides by inhibiting the mixed function oxidase enzymes primarily found in the liver but also located in other organs. MGK-264 is found in numerous insecticide formulations usually when the active ingredients are pyrethrins and pyrethroids but also may be found in some formulations with organophosphates and carbamate and other chemicals. Since MGK-264 is found in many pesticide formulations, its occurrence as residues on RACs and in interior structures is common. Because of its widespread use, exposure to applicators may be significant.

The structure of MGK-264 is as follows



[N-(2-ethylhexyl)-5-norborene-2,3-dicarboximide <u>or</u> N-octyl bicycloheptene dicarboximide]

D. Evaluation of Carcinogenicity Evidence:

1. Rat Carcinogenicity Study. IRDC Study No.: 551-030, October 8, 1993 MRID No.: 43005301, HED Document No.: 011100. Attachment 2.

a. <u>Experimental Design</u> Five groups of 60/sex Charles River CD^{R} strain rats were dosed as either control-1, control-2, 50, 150 or 450 mg/kg bw/day of MGK-264 in their diets for 24 months. The dietary levels of MGK-264 were adjusted based on the weight of the animals and their anticipated feed consumption. There were no interim sacrifices.

b. <u>Discussion of Tumor Data</u> The thyroid of male rats was noted to be associated with statistically significant increases in <u>follicular cell adenomas</u> in the 150 and 450 mg/kg/day dose groups and in combined adenomas and carcinomas in the 450 mg/kg/day dose group as indicated in Table 1 (adapted from Attachment 3).

Historical control data from the laboratory are not available at this time. The registrant has not responded to the Agency's request.

Historical control data obtained from the Charles River Breeding Laboratories (Spontaneous Neoplastic Lesions and Selected Non-neoplastic Lesions in the Crl:CD®BR Rat, February, 1992, prepared by Dr. Patricia L. Lang) indicated that in males from 19 studies thyroid follicular cell adenomas were at a 5.55% rate (69 incidents) with a range from 1.1 to 25.7% for those studies where a diagnosis was made. Tyroid follicular cell carcinomas had a rate of 1.29% (16 incidents) with a range from 1.0 to 17.4%.

c. Non-neoplastic Lesions The NOEL for this study was set at 50 mg/kg/day and the LEL was set at 150 mg/kg/day with there being indications of liver toxicity as indicated by increased liver (45.4% for males and 21.8% for females at 450 mg/kg/day) and hepatocyte hypertrophy (0%, 5%, 5%, 43.3% and 78.3% for males and 1.6%, 3.3%, 5%, 36.7% and 76.7% for females) for the control-1, control-2, 50, 150 and 450 mg/kg/day groups respectively. Portal bile duct proliferation, bile stasis and spongiosis hepatitis were also increased mainly in the high dose group. The high dose group also displayed kidney pathological changes (brown pigment) and changes in heart and brain weight.

Table 1. MGK-264 -Male Rat Thyroid Follicular Cell Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (mg/kg/day)			
	0	50	150	450
Adenomas	3/105	4[a]/56	**5/53**	**6/55**
(%)	(3)	(7)	(9)	(11)
p =	**0.040***	0.127	**0.032***	**0.018***
Carcinomas	2[b]/78	2/38	1/36	3/45
(%)	(3)	(5)	(3)	(7)
p =	0.128	0.228	0.479	0.098
Combined	5/105	6/56	6/53	9/55
(%)	(5)	(11)	(11)	(16)
p =	**0.014***	0.077	0.051	**0.004****

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
[a]First adenoma observed at week 66, dose 50 mg/kg/day.
[b]First carcinoma observed at week 93, dose 0 mg/kg/day.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential Survival was not affected by treatment. Body weight gain decreased in the high dose group generally starting probably after week 10 and reaching 16% in males and 43% in females for the interval of weeks 13 to 52. For the interval weeks 52-78, the high dose males gained 58% less and females gained approximately 50% less. Terminal body weights in the high dose were about 8% less for males and 18-21% less for females. It is probable that higher doses could have been tolerated.

2. Mouse Carcinogenicity Study. IRDC Study No.: 551-011, june 13, 1991, MRID No.: 42093802, HED Document No.: 009273. Attachment 4 is a copy of the DER.

a. Experimental Design Five groups of 50/sex CD-1 strain mice were dosed as control-1, control-2, 50, 400 and 800 mg MGK-264/kg bw/day for 79 to 80 weeks. Dose was adjusted to the body weight of the mice. There were no interim sacrifices.

b. Discussion of Tumor Data The 400 and 800 mg/kg/day dose male groups were associated with increased incidence of liver tumors (adenomas and adenomas and carcinomas combined). Only the 800 mg/kg/day dose group had increased adenomas. The high dose female groups was also associated with a statistically significant increase in combined adenomas and carcinomas. Tables 2 and 3 adapted for Attachment 3 illustrate the data.

Historical control data were not provided by the registrant in response to HED's request. Historical control data obtained from the Charles River Breeding Lab (Spontaneous Neoplastic Lesions in the Crl:CD-1®[ICR]BR Mouse, prepared by Dr. Patricia Lang for studies conducted between 1978 and 1984) indicate that in males hepatocellular adenoma there were 8.2% (41 incidents in 499 mice) with a range from 0 to 16.3% and for hepatocellular carcinoma there were 1.4% (7 incidents in 499 mice) with a range from 0 to 6.0% for 8 studies running for 18 months. **Thus, the high dose male group at 38% was in excess of the expected range and the 400 mg/kg at 16% was in the upper borders of the expected range.** In females, for adenomas there were 1.4% (7 incidents in 477 mice) with a range from 0 to 2.7% and for carcinomas there were 0.2% (one incident in 497 mice) with a range from 0 to 0.7%. **Females at 4% for adenomas were in excess of the range and the presence of a single carcinoma is considered rare and noted.**

Table 2. MGK-264 - Male Hepatocellular Tumor Rates+ in mice and Peto's Prevalence Test Results (p values)

	Dose (mg/kg/day)			
	0	50	400	800
Adenomas (%)	4/78 (5)	1/43 (2)	6[a]/38 (16)	12/32 (38)
p =	0.000**	0.756[n]	0.054	0.000**
Carcinomas (%)	2/86 (2)	1/46 (2)	3/44 (7)	1[b]/37 (3)
p =	0.310	0.516	0.175	0.499
Combined (%)	6/86 (7)	2/46 (4)	9/44 (20)	13/37 (35)
p =	0.000**	0.719[n]	0.023*	0.000**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
[n]Negative change from control.
[a]First adenoma observed at week 78, dose 400 mg/kg/day.
[b]First carcinoma observed at week 67, dose 800 mg/kg/day.

Table 3. MGK-264 - Female Mouse Hepatocellular Tumor Rates+ in mice and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	50	400	800
Adenomas (%)	0/90 (0)	0/50 (0)	1/48 (2)	2[a]/47 (4)
p =	0.032*	1.000	0.348	0.116
Carcinomas (%)	0/90 (0)	0/50 (0)	0/48 (0)	1[b]/47 (2)
p =	0.200	1.000	1.000	0.343
Combined (%)	0/90 (0)	0/50 (0)	1/48 (2)	3/47 (6)
p =	0.008**	1.000	0.348	0.039*

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.
[a]First adenoma observed at week 79, dose 800 mg/kg/day.
[b]First carcinoma observed at week 63, dose 800 mg/kg/day.

Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level. If *, then $p < 0.05$. If **, then $p < 0.01$.

c. Non-neoplastic Lesions The male liver was associated with "intrahepatic bile stasis" (10% and 90% in the mid and high doses vs 0% in the other groups); "hepatocellular hypertrophy (60% in the high dose group vs no more than 6% in the other groups); and biliary calculi (23% in the mid and 39% in the high vs no more than 4% in the other groups). Females had some increases in biliary calculi (6% in the mid dose and 18% in the high dose but 0% in all other groups) and hypertrophy (12% in the high dose group vs 0% in all other groups). See page 12 of the DER for full description.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential The only target organ recognized as being affected by treatment was the liver. Body weights were not recognized to be "toxicologically significantly different" by the study author and were of small (< 9%) magnitude. On this basis, higher doses could probably have been tolerated.

E. Additional Toxicology Data on MGK-264.

1. Metabolism Studies with labeled [hexyl -1-^{14}C] or [norbenene-2,3-^{14}C] MGK-264 indicated that the majority of the radioactivity was excreted in the urine and feces within 48 hours. After 7 days less than 0.5% radioactivity remained in the tissues with the intestines and liver retaining the largest fraction. Four major metabolites were found in the urine and feces.

2. Mutagenicity MGK-264 has been tested in several mutagenicity toxicity studies. Studies concluded to be acceptable have been submitted for bacterial mutagenicity, in vitro mammalian cell (L5178Y/TK cell line) forward mutation and unscheduled DNA synthesis. Additional genetic toxicity studies especially in vitro and in vivo chromosome aberration studies are considered desirable.

a) Salmonella assay - No evidence of mutagenicity in *salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 or TA100 were noted in the presence or absence of metabolic activation at dose levels of 100, 333, 667, 1000 or 3300 ug/plate.

b) Chromosome aberration studies. Two studies have been submitted but were considered to have study deficiencies (use of plastic vessels) and repeat studies have been requested. These studies, however, were not considered indicative of mutagenicity or genetic toxicity for MGK-264.

c) Unscheduled DNA synthesis. No evidence of unscheduled DNA synthesis was independently confirmed in two studies in rat hepatocytes at dose levels up to and including 50

ug/ml.

3. Developmental Toxicity. The rat developmental toxicity study demonstrated NOEL and LELs of 200 and 1000 mg/kg/day for maternal toxicity based on decreased body weight gain. Developmental toxicity was determined to have NOEL and LELs of 40 and 200 mg/kg/day based on increased resorptions and increased index of variants. No rabbit developmental toxicity has been submitted. The rat multi-generation reproduction study was determined not to have a LEL with there being increases in hepatocellular hypertrophy and decreased body weight during lactation at all dose levels including the lowest test dose of 1250 ppm.

4. Structure and Functional Activity Correlations

No specific structure activity relationships known at this time.

A factor to be considered under this category is the functional effect of MGK-264 as compared with piperonyl butoxide. Both of these chemicals inhibit mixed function oxidases and both produce similar non-neoplastic lesions in the liver of rats and mice and the hyperplasia and/or tumors in the follicular cells of the thyroid in rats.

5. Acute, Subchronic, and Chronic Toxicity Studies There are no currently acceptable acute toxicity studies with MGK-264. The acute oral LD_{50} has been reported as 2800 mg/kg (Farm Chemicals Handbook p. C 157). Subchronic oral studies were submitted as parts of the range finding studies for the rat and mice carcinogenicity studies. Chronic toxicity in dogs indicated NOEL and LELs of 7.5 and 33.7 mg/kg/day based on liver pathology. In rats,the systemic NOEL and LEL was determined to be 50 and 150 mg/kg/day based on liver weight increase and liver pathology (hypertrophy).

F. Weight of Evidence Considerations:

The committee will consider the following factors regarding the toxicology data on MGK-264 in a weight of evidence determination of carcinogenic potential.

1. *Rat and mouse carcinogenicity studies.*

Charles River CD strain rats were dosed as control (two groups), 50, 150 or 450 mg/kg/day of MGK-264 for 24 months. Survival was unaffected by treatment. Based on deceases in body

weight, particularly in the later months of the study, higher doses could have been tolerated. Adequacy of dosing needs to be resolved.

At 150 and 450 mg/kg/day thyroid follicular cell adenomas were in creased in males. The combination of adenomas and carcinomas were increased in the high dose group only.

CD-1 strain mice were dosed as control (two groups), 50, 400 and 800 mg/kg/day of MGK-264 for 79-80 weeks. Survival was not affected and body weight was only slightly decreased (i.e. < 9% at best). Higher doses could have been tolerated.

Hepatocellular adenomas in males in the 800 mg/kg/day high dose group were increased ($p < 0.001$) and adenomas and carcinomas combined in males were increased in the 400 ($p = 0.023$) and 800 ($p < 0.001$) mg/kg/day groups. In females, combined adenomas and carcinomas were increased ($p < 0.039$) in the 800 mg/kg/day group.

2. No specific structure activity relationships were found.

3. MGK-264 was not mutagenic or geneto toxic in the several studies presented.

ATTACHMENT 1

Summary Table of Two Rat and Mouse Studies with MGK-264.

Study Identification	Organs of Concern for Neoplasia
rat Study. IRDC Study No.: 551-030, October 8, 1993. Charles River CD Strain rats; two control groups,, 50, 150 and 450 mg/kg/day for two years.	Thyroid: follicular cell tumors in males. Based on body weight gain decreases, it needs to be resolved in the dose levels were adequate.
Mouse Study. IRDC Study No.: 551-011, June 13, 1991. CD-1 strain mice. Control, 50, 400 or 800 mg/kg/day for 18 months.	Liver: Both sexes at 400 and 800 mg/kg/day. Based on the liver being the only target organ affected and minimal changes in body weight, higher doses could have been tolerated.

J. Doherty
TOX I

ATTACHMENT 2

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

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JUL 12 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID No.: 057001. MGK-264: Review of a series 83-5 chronic toxicity/carcinogenicity study with rats. Request for historical control data for thyroid tumors.

TOX CHEM No.: 613
PC No.: 057001
Barcode No.: D197633
Submission No.: S455227

FROM: John Doherty John Doherty 7/8/94
Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO: Bruce Sidwell/Alan Dixon
Product Manager #53
Special Review and Reregistration Division (7508W)

THROUGH: Marion Copley, DVM, Section Head
Section IV, Toxicology Branch I
Health Effects Division (7509C) Linda F. Hansen (for) 7/11/94

I. CONCLUSION

The rat series 83-5 chronic feeding/carcinogenicity study (MRID No.: 430053-01, IRDC Study No.: 551-030, October 8, 1993) with MGK-264 was reviewed and determined to be CORE MINIMUM. No additional series 83-5 study data for MGK-264 are required at this time. The liver was identified as the primary target organ for toxicity responses and a systemic NOEL and LEL of 50 and 150 mg/kg bw/day was assigned based on liver weight increases accompanied by hepatocyte hypertrophy and other liver histopathology.

The study indicated possible compound related increases in thyroid adenomas and this issue will need to be addressed by HED's carcinogenicity Peer Review Committee to determine if the data support a conclusion that MGK-264 is carcinogenic in the

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rat. The registrant is requested to provide historical control data for incidence of thyroid follicular tumors in the strain of rat used for this study[1].

II. Action Requested

The McLaughlin Gormley King Company has submitted both a 13 week range finding study and a 24 month chronic feeding/ carcinogenicity study with rats to fulfill the requirements for the reregistration of the synergist MGK-264 (refer to letter from Marla Lenzen dated October 14, 1993). These studies are further identified in part IV below. The studies were reviewed and the following comments apply.

III. Toxicology Branch Comments

1. The thyroid was identified as a possible carcinogenic target for MGK-264. Refer to the DER for the illustration of the data. The issue of possible carcinogenicity of MGK-264 will be referred to the HED Carcinogenicity Peer Review Committee for classification and resolution of the possible effect in the thyroid.

The registrant is requested to provide HED with historical control data for the frequency of occurrence of thyroid follicular cell adenomas and carcinomas in the Charles River CD strain rat used for this study. The historical control data should consists of all studies conducted by the IRDC using this strain of rat for the past 10 years and any studies completed since the time of completion of the MGK-264 study. The rats should be from the same supplier (if possible). Each study should be listed separately with its study date, thyroid follicular adenoma and carcinoma data (number of tumors and number of animals examined) and information on preneoplastic conditions in this structure including hyperplasia and related lesions. A summary table expressing the total number of tumors and total number of animals examined is not sufficient by itself.

2. TB-I noted some tactical problems with the presentation of the study report. These are follows:

The assembly of the report using the plastic binders with multi holed paper resulted in the sheets separating from the package when the package was read. Since review work requires

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[1]The registrant is referred to the document entitled "Pesticide Reregistration Rejection Rate Analysis Toxicology" (EPA 738-R-93-004, July 1993) page 102 for the listing of the general requirements for submission of historical control data.

comparing the information on one page with information on other pages, the fragility of the binding hindered the process. It is strongly advised that future submissions utilize stronger binding material to hold the pages of the volumes of information together.

The structure of Table 14 which presents the results of the pathology analysis was also considered unnecessarily hard to use. The data were presented separately for the animals dying on study and for those sacrificed at termination. This resulted in the reviewer having to do much arithmetic to determine the total number of animals affected with a given lesion. Since death was not a result of treatment, the practice of separating the lesions from the animals dying on study and at sacrifice served no meaningful purpose. It is more important to indicate the total number of animals with a given type of lesion. The reviewer can do an animal by animal assessment if he wants to determine a time effect.

The structure of Table 13 of the study report which illustrates the organ weight data was also considered unnecessarily cumbersome. Most other study reports manage to include all of the data for each dose level for a given organ on a single page. The structure of this table required the reviewer to pursue the tabulations on adjacent pages. This together with the loose binding of the pages contributed to unnecessary delays.

IV. Studies Reviewed

Study Identification	Material	MRID No.:	Results	Classification
82-1. 13 week feeding (range finding study)-rats. IRDC, Study No.: 551-028, August 9, 1989	Technical MGK-264 Lot 7437, Purity 90.76 to 92.12%.	429706-01	[No separate DER prepared results are presented in the series 83-5 IRDC Study No.: 551-030, October 8, 1993]	SUPPLEMENTARY

83-5. Combined chronic feeding/carcinogenicity study-rats/ IRDC Study No.: 551-030 October 8, 1993	Technical MGK-264 Lot 7437, purity 90.76 to 92.12%	430053-01 (7 volumes)	Five groups of 60/sex Charles River CD[R] strain rats were dosed as either control (two separate groups), 50, 150 or 450 mg/kg bw/day of MGK-264 in their diets in a study designed to assess for chronic feeding toxicity and carcinogenicity effects. The 50 mg/kg/day group males had marginally increased (14% $p < 0.05$) terminal <u>liver weight</u> and higher dose levels had higher increases (maximum 45% for the high dose male and 59% for the female groups. At dose levels of 150 and above pathological changes in the <u>liver</u> (hepatocyte hypertrophy in both sexes and portal bile duct proliferation and bile stasis, spongiosis hepatitis and cysts in females) and <u>kidney</u> (brown pigment in females). At 450 mg/kg: additional liver pathology (bile duct proliferation, cysts and altered eosinophilic foci in males and spongiosis hepatitis in males) and kidney (brown pigment and cysts in males); kidney, heart and brain weights were increased. Several parameters were noted to be highest in the high dose test group especially for males but their association with treatment was indefinite (see DER for list). **The systemic LEL is 150 mg/kg based on increased liver weight supported by liver pathology (i.e. hepatocyte hypertrophy). The NOEL is 50 mg/kg/day.** The study did not indicate carcinogenic potential except for increased thyroid follicular tumors in males which indicated a response of 2, 1, 4, 5 and 6 for adenomas alone and 4, 1, 6, 7 and 9 for combined adenomas and carcinomas for the two control, low mid and high dose animals respectively (based on 60 per dose group). The issue of possible carcinogenicity based on thyroid data will be reviewed further by HED's Carcinogenicity Peer Review Committee.	MINIMUM

15

Reviewed by: John Doherty, Ph.D. John Doherty 7/8/94
Section IV, Tox. Branch (7509C)
Secondary Reviewer: Marion Copley, DVM
Section IV, Tox. Branch (7509C)

DATA EVALUATION REPORT

STUDY TYPE: 83-5. Chronic Feeding/oncogenicity-rats

TOX. CHEM. NO.: 613
PC No.: 057001

MRID NO.: 430053-01 (7 volumes)
429706-01 (range finding study)

TEST MATERIAL: Technical grade MGK-264, stated as being from lot 7437 and to be of 100% purity.

STUDY NUMBER: 551-030

SPONSOR: MGK Company

TESTING FACILITY: International Research and Development Corporation (IRDC)

TITLE OF REPORT: "24 month dietary chronic toxicity and oncogenicity study in the rat with MGK-264"

AUTHOR: Edwin I. Goldenthal, Ph.D.

REPORT ISSUED: October 8, 1993
[In life phase: Initiated January 15, 1990, terminal necropsy January 13-17, 1992.

Executive Summary:

Five groups of 60/sex Charles River CD^R strain rats were dosed for 24 months as either control (two separate groups), 50, 150 or 450 mg/kg bw/day of MGK-264 in their diets in a study designed to assess for chronic feeding toxicity and carcinogenicity effects.

The 50 mg/kg bw/day dose group males had marginally increased (14% $p < 0.05$) terminal liver weight and higher dose levels had higher increases (maximum 45% for the 450 mg/kg bw/day high dose male and 59% for the female groups. At dose levels of 150 mg/kg bw/day and above pathological changes in the liver (hepatocyte hypertrophy in both sexes and portal bile duct proliferation and bile stasis, spongiosis hepatitis and cysts in females) and kidney (brown pigment in females). At 450 mg/kg: additional liver pathology (bile duct proliferation, cysts and altered eosinophilic foci in males and spongiosis hepatitis in males) and kidney (brown pigment and cysts in males); kidney, heart and brain weights were increased. Several parameters were

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noted to be highest in the high dose test group especially for males but their association with treatment was indefinite (see DER for list). **The systemic LEL is 150 mg/kg bw/day based on increased liver weight supported by liver pathology (hepatocyte hypertrophy and other liver histopathology). The NOEL is 50 mg/kg bw/day.**

There was a possible carcinogenic effect characterized by increased thyroid follicular tumors in males which indicated a response of 2 (3.3%), 1 (1.7%), 4 (6.7%), 5 (8.3%0 and 6 (10%) for adenomas alone and 4 (6.7%), 1 (1.7%), 6 (10%), 7 (11.7%) and 9 (15%) for combined adenomas and carcinomas for the two control, 50, 150 and 450 mg/kg bw/day dose groups respectively (based on 60 per dose group). The issue of possible carcinogenicity based on thyroid data will be referred to the HED Carcinogenicity Peer Review Committee.

Classification: CORE MINIMUM. The structure of some of the tables made the report difficult to read (see page 13 of this DER). The study, however, satisfies the requirement for a series 83-5 chronic feeding/carcinogenicity study and no additional series 83-5 data are required at this time.

Quality Statement: Provided.
Good Laboratory Practice Statement: Provided.
Statement of No Data Confidentiality: No claim of data confidentiality asserted.

Review

Experimental Constants

Test material:

Chemical:	MGK-264, N-octylbicycloheptene dicarboximide.
Lot No.:	7437
Purity:	100% (as reported), actual analytical results as determined by the supplier (sponsor) 90.76 to 92.12 %. The identification of the impurities was not provided.
Description:	Pale yellow liquid
Source:	McLaughlin Gormley King Company

Analytical Chemistry. (Appendixes A, B, C, D and E of study report).

The stability, homogeneity and concentration of MGK-264 in the test diets was determined gas chromatographically.

Stability. Three target samples of 400, 2,000 and 15,000 "mg/ml" (an apparent misprint" yielded ratios of 1.00, 1.03 and 1.04 for day 14 to day 0 ratio for the analytical concentrations expressed in ppm. Thus, indicating that MGK-264 was stable in the test diet for 14 days.

Homogeneity. The 400, 2,000 and 15,000 ppm test diets were determined to have 408 ± 7.8 (c.v. = 1.9), 2,020 ± 94.3 (c.v. = 4.7) and 15,400 ± 653

(c.v. = 4.2) ppm respectively based on ten samplings. The low coefficient of variation (c.v.) resulting indicated an homogeneous sample. More detailed descriptions of the sampling procedure used should have been provided.

Concentration. Samplings of diets for each of the first four weeks and then for every fourth week thereafter were reported (total 29 sample preparations) for both male and female test diets. These resulted in means of 97% ± 3.4% to 99% ± 3.85% of the target diets. Generally the analyses were greater than 95% or less than 105%. Only one analysis was 87% for one week only (females at week 36).

In conclusion, the analytical data are within acceptable limits.

Test animals:

Species:	Rat
Strain:	Charles River CD^R
Supplier:	Charles River Breeding, Portage, Michigan
Age:	28 days on receipt, 46 days at start of dosing
Weight:	Males: 156-255: females: 129-192 gms at randomization.
Housing:	Individually.
Randomization:	Computer assisted Xybion Randomization procedure based on body weight.
Feed:	Certified Purina Rodent Chow #5002

Basic Experimental Design.

Five groups of 60/sex rats were dosed as control-1, control-2, 50, 150 and 450 mg/kg bw/day in the diet. The dietary levels of MGK-264 were adjusted based on the weight of the animals and anticipated feed consumption. The rats were dosed for a scheduled 24 months and there was no interim sacrifice included.

Basis for dose level selection. These dose levels were selected based on a preliminary 13 week range finding study (MRID No.: 429706-01, IRDC Study No.: 551-028, August 9, 1989, no DER has been prepared for this study). This study assessed the effects of control, 125, 250, 500, 1000 and 2000 mg/kg/day in Charles River CD^R strain rats (10/sex/dose group). This study was claimed by the authors to establish a NOEL for "toxic" effects of 500 mg/kg/day for both sexes. Reduced bodyweight was evident at 1000 mg/kg/day the LEL for "toxic" effects and deaths resulted in males and females (with males being more susceptible) at 2000 mg/kg/day. Liver weight was increased at dose levels of 250 mg/kg/day and above and was attributed by the author to "work hypertrophy". There were no indications of elevated serum enzymes or microscopic hypertrophy of the liver to indicate pathological changes reported.

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

Statistical Test	Parameter
Bartlett's test followed by t-statistic (equal or unequal variance), nonparametric analysis, when appropriate, using rank transformation.	Body weights Food consumption and efficiency Clinical pathology parameters Organ weights
Life Table test Hoel-Walburg test Fisher's Exact test Cochran-Armitage test	Tumor incidence data

METHODS AND RESULTS

1. Survival. The rats were reportedly assessed for mortality at least twice daily.

The study report asserts that there were no effects on mortality. There were 26, 26, 25, 24 and 31 males and 24, 25, 28, 19 and 27 females surviving to terminal sacrifice at week 105 for the control, control, 50, 150 and 450 mg/kg/day dose groups respectively.

2. Clinical signs. Once weekly detailed examinations of the rats were conducted in addition to the routine inspection for mortality and overt toxicity.

The study report asserts that there were no test article related increases in obvious clinical signs refer to Table 2 of the study report). There were also no obvious increases in palpable masses (refer to Table 3 of the study report. There was no evidence of intercurrent diseases that might have compromised the study.

3. Body weight. Body weight data were reportedly collected weekly for the first 14 weeks and every two weeks thereafter.

The study asserts that body weight in the high dose group only was decreased for both sexes. Consistent statistically significant differences were noted after week 18 for males and after week 10 for females. Final high dose group body weights were 8.7 or 8.4% for males and 20.9 or 17.5% for females less than control group 1 or 2.

The 150 mg/kg dose group was not reported to have statistically significant differences in body weight. Final body weights were 5.7 or 5.4% for males and 7.0 and 3.0% for females lower than control 1 or 2. All 50 mg/kg/day dose level values were higher than the controls (0.8 to 5%). These data suggest a

possible marginal or threshold effect in the 150 mg/kg/day dose group.

Table 1. illustrates body weight gain at selected intervals.

Table 1. Body weight gain (g) at selected intervals.

Interval (weeks)	Dose Level									
	Control	Control	50	150	450	Control	Control	50	150	450
	(mg/kg bw/day)									
0 - 13	310	304	305	308	293	139	140	154	141	128
13 - 52	160	163	165	153	134	120	113	116	108	69
52 - 78	52	53	36	38	22	77	58	74	53	34

Data are calculated based on data from Table 4 of the study report (pages 102 to 109). Data are in grams.

Body weight gain differences became most evident after week 13 and lesser gains were noted for the interval weeks 13-52 and 52 to 78. The decrease in weight gain in the 450 mg/kg/day dose group for the interval weeks 52 to 78 reached 58% in males and 50% in females. After week 78 all dose groups lost weight.

4. Food consumption, compound intake and feed efficiency. Food consumption data were reportedly collected weekly for the first 14 weeks and every two weeks thereafter.

Food consumption was decreased and generally statistical significance was attained for the high dose groups for females. Occasional differences in food consumption were noted for the other groups. There were no consistent differences in feed efficiency reported.

Compound intake was calculated to be essentially the same as the nominal dosages or 50.4, 151 or 454.3 mg/kg/day for males and 50.0, 149.6 or 449.7 mg/kg/day for females.

5. Ophthalmological examinations. Assessments were made once at pretest and at study termination. The eyes were dilated with 1% tropicamide and a binocular indirect ophthalmoscope was utilized with a 20 diopter focusing and magnifying lens to assess for effects.

No test article related effects were noted.

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Clinical Laboratory assessments were made at 6, 12, 18 and 24 months. Blood was obtained from the orbital sinus from 10 rats/sex following overnight fasting. Water was available during fasting and urine was collected for future analysis.

6. Hematology. The following parameters were assessed.

x	Hematocrit (HCT)	x	Leukocyte differential count
x	Hemoglobin (HGB)	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)	x	Mean corpuscular HGB conc.(MCHC)
x	Erythrocyte count (RBC)	x	Mean corpuscular volume (MCV)
x	Platelet count	x	Reticulocyte count

Note: No assessment for clotting efficiency was made.

No test article related effects were noted.

7. Clinical Chemistry.

	Electrolytes:		Other:
x	Calcium	x	Albumin
x	Chloride	x	Blood creatinine
	Magnesium	x	Blood urea nitrogen
x	Phosphorous	x	Cholesterol
x	Potassium	x	Globulins
x	Sodium	x	Glucose
	Enzymes	x	Total Bilirubin
x	Alkaline phosphatase	x	Total Serum Protein
	Cholinesterase		Triglycerides
x	Creatinine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase	x	Albumin/globulin ratio
x	Serum alanine aminotransferase (also SGPT)		
x	Serum aspartate aminotransferase (also SGOT)		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

No consistent statistically significant increases in these parameters were noted. Some "slight" increases in cholesterol, total protein and globulin at the 12th month interval were noted for the high dose group but these are not considered by TB-I (or the study author) to be meaningful.

8. Urinalysis.

x	Appearance	x	Glucose
x	Volume	x	Ketones
x	Specific gravity	x	Bilirubin
x	pH	x	Blood
x	Sediment (microscopic)	x	Nitrate (nitrite)
x	Protein	x	Urobilinogen
x	Leukocytes		

No changes in the composition of the urine were attributed to treatment.

9. Organ Weights. The following organs were selected for weighing.

adrenals (2)	liver
brain (with stem)	ovary (2)
heart	spleen
kidney (2)	testis (2)

Absolute liver weight was increased for all three male dose groups. Apparent increases in the high dose groups only for the kidney, heart and brain were reported. Table 1 below illustrates the weight effects in the liver as determined at terminal sacrifice. The kidney, heart and brain are discussed separately below.

Liver. The liver weight data are illustrated in Table 2 below. In addition to the data shown in Table 2, the liver weight relative to brain weight was also calculated and the same pattern of effect was noted. Based on these data the low dose male group was statistically significantly increased for absolute weight and the relative weights were also increased (12% for relative to body and 11% for relative to brain).

Table 2. Terminal liver weight in rats dosed with MGK-264 for two years

	Males		Females	
Group	Absolute[1]	Relative[2]	Absolute	Relative
Control-1	19.40 ± 3.36	3.32 ± 0.97	17.09 ± 5.03	3.65 ± 0.93
Control-2	20.31 ± 4.19	3.40 ± 0.70	15.56 ± 3.2	3.61 ± 0.68
50 mg/kg/day	**14.2%*/9.1%**	12%/9%	-1%/8.2%	-1%/--
150 mg/kg/day	**15.6%*/10.4%**	**21%*/18%**	8.8%/19.5%	**22%/24%***
450 mg/kg/day	**45.4%**/38.8%****	**59%**/55%****	**21.8%*/33.7%****	**61%**/63%****

Data are from Table 13 page 204-5 (males) and 212-3 (females).
1. Data are for the control groups the weight in gms ± the standard deviation. For the dosed groups the percentage difference relative to the first control group/the second control group. It should be noted that the dosed groups had standard deviations similar to the control groups (i.e. about 15%)
2. Liver weight relative to body weight. Absolute values are presented for the controls but the percentage relative to the controls for the dosed animals are presented.
* $p < 0.05$, ** $P < 0.01$.

Kidney. For the male high dose group. both the left (32%, $p < 0.01$ and 34%, $p < 0.05$, for the first and second control groups respectively) and right (25%, $p < 0.05$, second control group only) were increased for absolute weight. The relative weights both to body weight and brain weights were also statistically significantly increased for the high dose males only. Only kidney weight relative body weight was increased (left: 29% and 23% and right: 31% and 22%, $p < 0.05$ or < 0.01)

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for the females. Thus, TB-I concludes that the high dose group is affected especially in males with regard to an increase in kidney weight.

Brain. Brain to body weight was increased in the female high dose group (28%, $p < 0.01$ and 20%, $p < 0.05$) and males were as much as 11% higher but not significant.

Heart: The heart to body weight ratio for the high dose females was increased (25%, $p < 0.01$ and 17%, $p < 0.05$). The male high dose group was as much as 15% higher but statistical significance was not attained.

TB-I considers that the changes in brain and heart weight are reflective of the decreased body weight since there were no accompanying pathological changes.

10. Pathology (necropsy and histopathology).

Sacrifice and Pathology The surviving rats were sacrificed with carbon dioxide asphyxiation. All survivors were subjected to necropsy. The tissues were fixed in formalin (except the eyes were fixed in glutaraldehyde fixative and the testis in Bouin's fluid). The following tissues were indicated in the protocol as being preserved.

	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	x	Aorta	x	Brain (fore, mid, hind)
x	Salivary glands	x	Heart	x	Periph. nerve (sciatic)
x	Esophagus	x	Bone marrow(femur)	x	Spinal cord (3 levels)
x	Stomach (g and ng)	x	Lymph nodes	x	Pituitary
x	Duodenum	x	Spleen	x	Eyes (optic n.)
x	Jejunum	x	Thymus (region)		Glandular
x	Ileum		Urogenital	x	Adrenals (cortex and med)
x	Cecum	x	Kidneys		Lacrimal gland
x	Colon	x	Urinary bladder	x	Mammary gland (region)
x	Rectum	x	Testes	x	Parathyroids
x	Liver (ea. lobe)	x	Epididymides	x	Thyroids
	Gall bladder	x	Prostate		Other
x	Pancreas	x	Seminal vesicle		Bone
	Respiratory	x	Ovaries	x	Skeletal muscle
x	Trachea	x	Uterus	x	Skin
x	Lung	x	Vagina	x	All gross lesions and masses
	Nose				
	Pharynx				
	Larynx				

In addition to the above tissues, the following were indicated as benign examined as per reports of lesions noted in Table 14: Bone (femur, rib, skull and tibia), clitoral gland, ear, fat (omental), lacrimal gland. lip, lymph nodes (several), mammary region, mesentery, nasal tissues, oral tissue, penis, pericardium, prepuce, preputial gland, skin (ear, nose, tail), soft palate, soft tissue (abdomen, foot, head. leg),

The tissues were described as being sectioned at 5

microns and stained with hematoxylin and eosin for animals in the control and 450 mg/kg/day groups and for all animals dying or sacrificed. The liver and thyroid/parathyroid, lungs, kidneys, tissue masses (and adjacent drainage lymph nodes) and gross lesions form all animals at terminal sacrifice were reportedly assessed histopathologically.

The study report asserts that only the liver and thyroid exhibited reactions or possible reaction to treatment. The following tissues/organs are discussed individually.

A. Liver. Liver weight was increased (refer to Table 2 above) and the liver was the only organ reported to have gross necropsy lesions (tan and white foci in both sexes at 450 mg/kg/day and increased cysts in females in the 150 and 450 mg/kg/day dose groups). Table 3 illustrates the lesions noted in the liver by histological examination.

Table 3. Selected histopathological findings in the liver of rats dosed for up to two years with MGK-264.

Lesion description	Males[1] mg/kg bw/day					Females[1] mg/kg bw/day				
	0_1	0_1	50	150	450	0_1	0_2	50	150	450
Hepatocyte hypertrophy	0	3	3	**26**	**47**	1	2	3	**22**	**46**
Portal bile duct proliferation	43	39	39	47	**52**	25	28	31	35	**51**
Bile stasis	0	0	0	0	**20**	0	0	0	1	**23**
Spongiosis hepatitis	25	19	25	26	**40**	4	2	4	**8**	**11**
Altered foci, eosinophilic	3	1	6	5	16	3	1	8	7	9
Cysts	2	0	1	1	4	1	2	0	5	8
Hepatocellular Adenoma	0	0	2	0	1	0	0	0	1	2
Hepatocellular Carcinoma	1	2	1	1	1	1	1	0	0	0

Data are from Table 14 pages 230 to 232 for males and 269 to 271 for females.
1. Based on the original 60 rats/sex/dose group.

Table 3 establishes that the NOEL and LEL for liver pathology changes is 50 and 150 mg/kg in both sexes based primarily on hepatocyte hypertrophy.

The lesion portal bile duct proliferation was elevated in females the mid (150 mg/kg/day) and both sexes high dose

group. The high dose group also had more animals with the proliferation described as mild as opposed to the other groups which were mostly described as trace. Bile stasis (characterized as reddish brown calculi within intrahepatic bile ducts in portal areas) was also elevated in the high dose group and one animal in the mid dose female group was affected to support the position that the bile duct is affected at the mid dose group as indicated by the proliferation in females. Spongiosis hepatitis was elevated in the mid and high dose females and high dose males. This is considered by TB-I to be possibly related to indirect effects of the test material. There is an increase in cysts in the mid and high dose females and high dose males. TB-I considers this unusual and cannot rule out the relationship of dosing with the increased presence of cysts even though the relationship may be indirect.

The lesion "altered foci, eosinophilic" is increased in the high dose group for males. TB-I notes that both males and females in the low dose group have more incidence of this lesion than either of the controls but there is no dose response over the broad range of dosing (50 to 450 mg/kg/day).

The liver tumors (hepatocellular adenoma and carcinoma) did not show evidence of compound related increases.

In addition to the lesions listed in Table 2 above, the following lesions were considered to be elevated in the high dose group (male and/or female). Their relationship to treatment or their toxicological significance is considered equivocal by TB-I. Each item is discussed as follows:

Hepatocyte vacuolation-multifocal-Among the males the control and lower dose groups had 13 to 15 incidents, the high dose group had 23 incidents. The high dose group females had the lowest incidence of all groups female groups.

Altered foci, clear cell-The males in the high dose group had 18 animals affected, one control group had 11 incidents, all other groups were lower. The females did not have any indication of a compound related increase with there being 9 in the high dose group, 8 in one control group although the second control group and the other groups all had 5 incidents.

Cholangiofibrosis-The high dose group for each sex had the highest incidence. The high dose males had 24 incidents as compared to 17 and 16 in the controls. The high dose female group had 21 incidents as compared to 11 and 16 in the controls. The mid dose female group had 20 incidents. TB-I has determined that at best a possible effect of treatment resulted.

B. Kidney. Kidney weight was increased. Table 4 below illustrates selected pathological findings in the kidney. The incidence of "brown pigment" in the kidneys was increased. Both

the mid and high dose group is considered to be affected in females. Most of the cases were described as trace but in the high dose group, 9 were described as mild. The females also had markedly less "pelvic mineralization" 57% in both controls, 45% in the low dose group, 37% in the mid dose group and 27% in the high dose group. The high dose male group also had a lower incidence of this condition. A decrease in "pelvic mineralization" is not considered by TB-I to be a toxicity response and the data are illustrated for possible future reference.

Among the males, there were more cysts in the high dose group (13) than in any other group (5-7). The severity of the cysts were also described as "severe" only in the mid and high dose groups. Brown pigment was present (described as trace) only in the high dose group which had four rats affected.

TB-I concludes that the NOEL and LEL for kidney effects is 50 and 150 mg/kg/day. At 150 mg/kg/day there is increased "brown pigment" in females. At 450 mg/kg/day. There are increases cysts and a threshold level for increase in "brown pigment" in males.

Table 4. Histopathological finding in the kidney in rats dosed for up to two years with MGK-264.

Lesion description	Males[1]					Females				
	0_1	0_1	50	150	450	0_1	0_2	50	150	450
Brown pigment	0	0	0	0	4	1	1	4	11	33
Cysts	7	7	5	7	13	2	1	3	2	1
Pelvic mineralization	10	5	9	9	5	34	34	27	22	16

Data are from Table 14 pages 227 - 228 for males and 267 -268 for females.
1. Based on the original 60 rats/sex/dose group.

C. Thyroid. The thyroid was identified by the study author as having "increased incidence of adenomas of the follicular epithelium" in males. No increase in thyroid tumors were noted in the females. Table 5 below illustrates the pathological findings in the thyroid.

As indicated in Table 5, there is an apparent test material related increase in follicular adenomas in males and when follicular adenomas and carcinomas are combined, there is also an apparent increase. Historical control data for this strain of rat were not provided in the study report. The conclusion for there being a definite compound effect for increased thyroid tumors will be deferred to the HED Carcinogenicity Peer Review Committee.

C-cell adenomas, carcinomas and hyperplasia did not show any indication of increases with the dose level, The lowest incidence of hyperplasia was in the high dose group and there were no adenomas or carcinomas in the high dose group.

Table 5. Histopathological finding in the thyroid of rats dosed for up to two years with MGK-264.

Lesion description	Males[1]					Females				
	0_1	0_1	50	150	450	0_1	0_2	50	150	450
Follicular adenoma	2	1	4	5	6	2	1	1	1	2
Follicular carcinoma	2	0	2	1	3	0	1	0	1	0
Combined[2]	4	1	6	~~4~~ 6	9	2	1	1	2	2

Data are from Table 14 pages 257 for males and 291 females.
1. Based on the original 60 rats/sex/dose group but one control and 2 low dose males were too autolyzed for diagnosis.
2. Rats with a carcinoma and an adenoma are counted only in the group with carcinomas.

D. Heart. Heart weight was increased. No test chemical related increases in lesions were noted. In males the highest incidence of "vascular mineralization" was in the high dose group (8 incidents) with there being 4 or less in all other groups. In females this condition was not present in the high dose group but there were 1 to three incidents in all other groups. TB-I declines to associate the higher rate in males in the high dose group with treatment.

E. Brain. Brain weight was increased. No test chemical related lesions were judged to be present. There was a single incident of benign granular cell tumor in the high dose males, but TB-I declines from associating its presence with treatment. It was also noted that the high dose male and female had "malacia" which was described as moderate (female) and severe (male). Only one other animal (a control male, described as moderate) had this condition.

F. Miscellaneous lesions with highest incidence in the high dose group of males and/or females.

The following tissues were noted to have the highest incidence of certain types of lesions in the high dose group only. Males and or females were affected and in some cases the severity of the lesion was also noted to be higher in the high dose group.

-adrenal medulla - hyperplasia (males only)
-bone - osteoarthritis (males only)

-bone marrow - myeloid hyperplasia (males only)
-eye - retinal atrophy (males and females)
-eye - keratitis, acute (males only)
-lung - pneumonia (males only)
-lymph node mediastinal - hemorrhage (males only)
-pancreas - acinar hypertrophy (males only)
-parathyroid - hyperplasia (males only, severity increased)
-skin - kertocanthoma (males)
-stomach - mineralization (males, severity increased)
-testis - arteritis
-urinary bladder - epithelial hyperplasia (males)
-ovary - cysts

Although the high dose group had the highest incidence of these lesions their exact relationship to the test material cannot be ascertained but are listed above for possible future reference. In most cases they were only slightly higher than the other groups but in some cases were more than twice as high as the controls. In any case since the NOEL and LEL are set at lower dose levels, these conditions will not impact regulatory aspects of MGK-264. None of these were considered definitely related to treatment by the study author.

CONCLUSIONS This study is classified as CORE MINIMUM. The limiting factor is that the study did not establish a definite NOEL for increases in liver weight in males. TB-I considers that the low dose (50 mg/kg bw/day) is a threshold no effect level since there was no corresponding histopathology or other signs of toxicity at this level and the males were statistically significantly increased when compared to only one of the two concurrent control groups. For regulatory purposes, TB-I assigns a LEL of 150 mg/kg/day. At this dose level the liver weight increase is supported by pathological changes (hepatocyte hypertrophy and other lesions) and the NOEL is 50 mg/kg/day although a slight increase (14%) is noted in males it was not accompanied by hypertrophy.

Study Deficiencies No major study deficiencies were noted. Some comments on the presentation of the study are as follows. The body weight in terms of weight gain should have been calculated and discussed by the study author. Historical control data for the thyroid tumors should have been included in the report since this gland showed possible compound related increases in frequency.

TB-I notes, however, that the assembly of the report using the plastic binders with multi holed paper resulted in the sheets separating from the package when the package was read. Since review work requires comparing the information on one page with information on other pages, the fragility of the binding hindered the process. It is strongly advised that future submissions utilize stronger binding material to hold the pages of the

volumes of information together.

The structure of Table 14 which presents the results of the pathology analysis was also considered unnecessarily hard to use. The data were presented separately for the animals dying on study and for those sacrificed at termination. This resulted in the reviewer having to do much arithmetic to determine the total number of animals affected with a given lesion. Since death was not a result of treatment, the practice of separating the lesions from the animals dying on study and at sacrifice served no meaningful purpose. It is more important to indicate the total number of animals with a given type of lesion. The reviewer can do an animal by animal assessment if he wants to determine a time effect.

The structure of Table 13 of the study report which illustrates the organ weight data was also considered unnecessarily cumbersome. Most other study reports manage to include all of the data for each dose level for a given organ on a single page. The structure of this table required the reviewer to pursue the tabulations on adjacent pages. This together with the loose binding of the pages contributed to unnecessary delays.

ATTACHMENT 3

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

JAN 17 1995

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: MGK-264 Qualitative Risk Assessment Based On Charles River CD Rat and Charles River CD-1 Mouse Dietary Studies

Caswell No. 613

TO: John D. Doherty, Toxicologist
Review Section IV
Toxicology Branch I
Health Effects Division (7509C)

FROM: Lori L. Brunsman, Statistician
Statistics Section
Science Analysis Branch
Health Effects Division (7509C)

THROUGH: Hugh M. Pettigrew, Section Head
Statistics Section
Science Analysis Branch
Health Effects Division (7509C)

Summary

This qualitative risk assessment of MGK-264 was based upon two chronic carcinogenicity studies conducted in Charles River CD rats and CD-1 mice. The rats were fed 0, 50, 150, or 450 mg/kg/day of MGK-264 for 105 weeks. The mice were fed 0, 50, 400, or 800 mg/kg/day of MGK-264 for 79 weeks.

The statistical evaluation of mortality indicated a significant decreasing trend with increasing doses of MGK-264 in male rats. Female rats showed no significant incremental changes in mortality with increasing doses of MGK-264.

Male rats had significant dose-related increasing trends in thyroid follicular cell adenomas and combined adenomas and/or carcinomas. There was a significant difference in the pair-wise comparison of the 150 mg/kg/day dose group with the controls for thyroid follicular cell adenomas. There were also significant differences in the pair-wise comparisons of the 450 mg/kg/day dose group with the controls for thyroid follicular cell adenomas and combined adenomas and/or carcinomas.

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There were no significant compound-related tumors observed in female rats.

The statistical evaluation of mortality indicated a significant increasing trend with increasing doses of MGK-264 in male mice. Female mice showed no significant incremental changes in mortality with increasing doses of MGK-264.

Male mice had significant dose-related increasing trends in hepatocellular adenomas and combined adenomas and/or carcinomas. There was a significant difference in the pair-wise comparison of the 400 mg/kg/day dose group with the controls for combined hepatocellular adenomas and/or carcinomas. There were also significant differences in the pair-wise comparisons of the 800 mg/kg/day dose group with the controls for hepatocellular adenomas and combined adenomas and/or carcinomas.

Female mice had significant dose-related increasing trends in hepatocellular adenomas and combined adenomas and/or carcinomas. There was a significant difference in the pair-wise comparison of the 800 mg/kg/day dose group with the controls for combined hepatocellular adenomas and/or carcinomas.

Background

A chronic dietary toxicity and carcinogenicity study in Charles River CD rats was conducted by International Research and Development Corporation, Mattawan, Michigan, for McLaughlin Gormley King Company, Minneapolis, Minnesota, and dated October 8, 1993 (Study No. 551-030; MRID No. 430053-01).

The study design randomly assigned groups of 60 rats per sex to two separate control groups and to dose levels of 50, 150, and 450 mg/kg/day of MGK-264 for 105 weeks. Pair-wise comparisons of mortality and tumor rates indicated no statistically significant differences between the two control groups in either sex. Therefore, the control groups have been combined for these analyses.

A chronic dietary carcinogenicity study in Charles River CD-1 mice was conducted by International Research and Development Corporation, Mattawan, Michigan, for McLaughlin Gormley King Company, Minneapolis, Minnesota, and dated June 13, 1991 (Study No. 551-011; MRID No. 420938-02).

The study design randomly assigned groups of 50 mice per sex to two separate control groups and to dose levels of 50, 400, and 800 mg/kg/day of MGK-264 for 79 weeks. Pair-wise comparisons of mortality and tumor rates indicated no statistically significant differences between the two control groups in either sex. Therefore, the control groups have been combined for these analyses.

Survival Analyses

The statistical evaluation of mortality indicated a significant decreasing trend with increasing doses of MGK-264 in male rats. Female rats showed no significant incremental changes in mortality with increasing doses of MGK-264. See Tables 1 and 2 for rat mortality test results.

The statistical evaluation of mortality indicated a significant increasing trend with increasing doses of MGK-264 in male mice. Female mice showed no significant incremental changes in mortality with increasing doses of MGK-264. See Tables 4 and 5 for mouse mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

Male rats had significant increasing trends in thyroid follicular cell adenomas and combined adenomas and/or carcinomas, both at $p < 0.05$. There was a significant difference in the pair-wise comparison of the 150 mg/kg/day dose group with the controls for thyroid follicular cell adenomas at $p < 0.05$. There were also significant differences in the pair-wise comparisons of the 450 mg/kg/day dose group with the controls for thyroid follicular cell adenomas at $p < 0.05$ and combined adenomas and/or carcinomas at $p < 0.01$.

There were no significant compound-related tumors observed in female rats.

Male mice had significant increasing trends in hepatocellular adenomas and combined adenomas and/or carcinomas, both at $p < 0.01$. There was a significant difference in the pair-wise comparison of the 400 mg/kg/day dose group with the controls for combined hepatocellular adenomas and/or carcinomas at $p < 0.05$. There were also significant differences in the pair-wise comparisons of the 800 mg/kg/day dose group with the controls for hepatocellular adenomas and combined adenomas and/or carcinomas, both at $p < 0.01$.

Female mice had significant increasing trends in hepatocellular adenomas at $p < 0.05$ and combined adenomas and/or carcinomas at $p < 0.01$. There was a significant difference in the pair-wise comparison of the 800 mg/kg/day dose group with the controls for combined hepatocellular adenomas and/or carcinomas at $p < 0.05$.

The statistical analyses of the male rats were based upon Peto's prevalence test since there was a statistically significant negative trend for mortality in male rats with increasing doses of MGK-264. The statistical analyses of the male mice were based upon

Peto's prevalence test since there was a statistically significant positive trend for mortality in male mice with increasing doses of MGK-264. The statistical analyses of the female mice were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Table 3 for rat tumor analysis results, and Tables 6 and 7 for mouse tumor analysis results.

Table 1. MGK-264 - Charles River CD Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks 1-26	27-52	53-78	79-105[f]	Total
0	3/120	6/117	14/111	45/97	68/120 (57)[*n]
50	1/60	0/59	8/59	26/51	35/60 (58)
150	2/60	1/58	10/57	23/47	36/60 (60)
450	1/60	1/59	3/57[a]	22/53[b]	27/58 (47)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 105.

[n]Negative trend.

[a]One accidental death at week 57, dose 450 mg/kg/day.

[b]One accidental death at week 79, dose 450 mg/kg/day.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. MGK-264 - Charles River CD Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks 1-26	27-52	53-78	79-105[f]	Total
0	0/120	3/120	10/117	57/106[a]	70/119 (59)
50	0/60	0/60	15/60	17/45	32/60 (53)
150	1/60	1/59	13/58	26/45	41/60 (68)*
450	0/60	0/60	5/60	27/54[b]	32/59 (54)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 105.

[a]One accidental death at week 104, dose 0 mg/kg/day.

[b]One accidental death at week 79, dose 450 mg/kg/day.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. MGK-264 - Charles River CD Rat Study

Male Thyroid Follicular Cell Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (mg/kg/day)			
	0	50	150	450
Adenomas (%)	3/105 (3)	4[a]/56 (7)	5/53 (9)	6/55 (11)
p =	0.040*	0.127	0.032*	0.018*
Carcinomas (%)	2[b]/78 (3)	2/38 (5)	1/36 (3)	3/45 (7)
p =	0.128	0.228	0.479	0.098
Combined (%)	5/105 (5)	6/56 (11)	6/53 (11)	9/55 (16)
p =	0.014*	0.077	0.051	0.004**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 66, dose 50 mg/kg/day.

[b]First carcinoma observed at week 93, dose 0 mg/kg/day.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. MGK-264 - Charles River CD-1 Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks 1-26	27-52	53-67	68-80[f]	Total
0	2/99[a]	2/97	8/95	8/86[a]	20/98 (20)*
50	1/50	1/49	2/48	5/46	9/50 (18)
400	0/50	1/49[b]	5/48	7/43	13/49 (27)
800	0/50	3/49[c]	11/46	3/35	17/49 (35)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 79.

[a]Two accidental deaths, one each at weeks 5 & 69, dose 0 mg/kg/day.

[b]One accidental death at week 52, dose 400 mg/kg/day.

[c]One accidental death at week 43, dose 800 mg/kg/day.

( ) Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 5. MGK-264 - Charles River CD-1 Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks 1-26	27-52	53-67	68-80[f]	Total
0	1/98[a]	7/97	6/90	12/84	26/98 (27)
50	0/50	0/50	3/50	0/47	3/50 (6)**
400	1/50	1/49	3/48	9/44[b]	14/49 (29)
800	1/49[c]	1/48	7/47	6/40	15/49 (31)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 79.

[a]Two accidental deaths, one each at weeks 4 & 12, dose 0 mg/kg/day.

[b]One accidental death at week 77, dose 400 mg/kg/day.

[c]One accidental death at week 7, dose 800 mg/kg/day.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 6. MGK-264 - Charles River CD-1 Mouse Study

Male Hepatocellular Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (mg/kg/day)			
	0	50	400	800
Adenomas	4/78	1/43	6[a]/38	12/32
(%)	(5)	(2)	(16)	(38)
p =	0.000**	0.756[n]	0.054	0.000**
Carcinomas	2/86	1/46	3/44	1[b]/37
(%)	(2)	(2)	(7)	(3)
p =	0.310	0.516	0.175	0.499
Combined	6/86	2/46	9/44	13/37
(%)	(7)	(4)	(20)	(35)
p =	0.000**	0.719[n]	0.023*	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[n]Negative change from control.

[a]First adenoma observed at week 78, dose 400 mg/kg/day.

[b]First carcinoma observed at week 67, dose 800 mg/kg/day.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 7. MGK-264 - Charles River CD-1 Mouse Study

Female Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	50	400	800
Adenomas (%)	0/90 (0)	0/50 (0)	1/48 (2)	2[a]/47 (4)
p =	0.032*	1.000	0.348	0.116
Carcinomas (%)	0/90 (0)	0/50 (0)	0/48 (0)	1[b]/47 (2)
p =	0.200	1.000	1.000	0.343
Combined (%)	0/90 (0)	0/50 (0)	1/48 (2)	3/47 (6)
p =	0.008**	1.000	0.348	0.039*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[a]First adenoma observed at week 79, dose 800 mg/kg/day.

[b]First carcinoma observed at week 63, dose 800 mg/kg/day.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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SECTION HEAD

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

ATTACHMENT 4
009273

FEB 19 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

6(A)(2)

MEMORANDUM

SUBJECT: EPA Id. No.: 57001-001021. MGK-264: Review of a mouse carcinogenicity study submitted as 6(a)2 data. Evidence for compound related increases in mouse liver tumors.

TOX CHEM No.: 613
PC No.: 057001
TOX PROJECT No.: 2-0675 and 2-0676
Submission No.: S407901 (for both)

FROM: John Doherty, PhD. 2/13/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Christine Rice/Veronica Dutch
Product Manager #52
Special Review and Reregistration Division
(H7508C)

THROUGH: Marion Copley, DVM, Section Head 2/13/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

KB 2/14/92

I. CONCLUSION

The mouse carcinogenicity study with MGK-264 was reviewed and it was noted that apparent compound related increases in liver adenomas especially in males dosed with 400 and 800 mg/kg/day were evident. Liver adenomas and a carcinoma which are rare in females were also present in this sex although not statistically significant. MGK-264 will be reviewed by the HED Carcinogenicity Peer Review Committee to determine the significance of this tumor and the carcinogenicity classification for this chemical.

The study was determined to be CORE GUIDELINE and satisfies the requirement for and 83-2 carcinogenicity study with mice. No immediate regulatory action affecting existing registrations and/or tolerances is necessary as a result of this

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6(a)2 submission.

II. Action Requested.

The McLaughlin Gormley and King Company has submitted a 18 month mouse carcinogenicity study with the insecticide synergist MGK-264 as a part of the reregistration data requirements for this chemical. The study has been reviewed and the DER is attached.

III. Toxicology Branch Comments.

1. The NOEL/LEL for this study was based on liver and gall bladder pathology and liver weight changes.

In addition to the liver toxicity, Toxicology Branch considered the apparent dose related increase in the presence of mineralization in the kidney to be an equivocal finding. There was only a net of 2% in the controls but 20% in the high dose group and the low (12%) and mid (18%) dose groups were also affected. The condition was described as "trace" for all dose groups and there was no dose related increase in severity. Toxicology Branch does not consider that this observation should be included in the NOEL/LEL setting for this study at this time since the severity did not increase with time or dose. It is recommended, however, that the rat and dog chronic feeding studies be carefully evaluated by future toxicology reviewers for this condition to help resolve the equivocal nature of this observation in mice.

2. Study reviewed.

Study Identification	TB-I Conclusions.
83-2. Oncogenicity - mice. IRDC Study No.: 551-011, June 13, 1991 (report issued). MRID No.: 420938-02 (5 volumes). Classification: GUIDELINE.	NOEL/LEL = 50/400 mg/kg/day. 400 mg/kg/day: Liver weight increases and gall bladder calculi in males and females; and liver/bile duct stasis in males. 800 mg/kg/day: additional liver pathology (bilary calculi, hepatocellular hypertrophy and hyperplastic nodules in males and females; in males only: portal bile duct proliferation, portal mono-nuclear cell infiltration, spongiosis hepatis (degenerative lesion), cysts and vacuolar change. Liver adenomas apparently increased in males and liver tumors (adenomas and a carcinoma) appear to present in females dosed with 400 and 800 mg/kg/day. Significance of these findings will be reviewed by the Carcinogenicity Peer Review Committee. Dose levels tested 0, 50, 400 and 800 mg/kg/day. CD-1 mice.

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[83-2. MGK-264 (1991)]

Reviewed by: John Doherty, Ph.D. John Doherty 2/13/92
Section IV, Tox. Branch (H7509C)
Secondary reviewer: Marion Copley, DVM Marion Copley 2/13/92
Section IV, Tox. Branch (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 83-2. Carcinogenicity - mouse.

MRID No.: 420938-02 (5 volumes) TOX. CHEM. No.: 613
PC. No.: 057001

TEST MATERIAL: MGK® 264, an insecticide synergist (N-octyl bicycloheptene dicarboximide),

STUDY NUMBER(S): IRDC Laboratory Project Identification 551-011.

SPONSOR: MGK (McLaughlin Gormley and King Company)

TESTING FACILITY: International Research and Development Co. (IRDC).

TITLE OF REPORT: "Eighteen month dietary oncogenicity study in mice with MGK® 264 insecticide synergist"

AUTHOR: Malcolm Blair, PhD.

REPORT ISSUED: June 13, 1991. Study in-life dates December 4, 1986 to June 2-9, 1988.

CONCLUSIONS:

NOEL/LEL = 50/400 mg/kg/day. 400 mg/kg/day: Liver weight increases and gall bladder calculi in males and females; and liver/bile duct stasis in males. 800 mg/kg/day: additional liver pathology (biliary calculi, hepatocellular hypertrophy and hyperplastic nodules in males and females; in males only: portal bile duct proliferation, portal mononuclear cell infiltration, spongiosis hepatis (degenerative lesion), cysts and vacuolar change.

Liver adenomas increased males and liver tumors (adenomas and/or carcinoma) present in females in 400 and 800 mg/kg/day.

Dose levels tested 0, 50, 400 and 800 mg/kg/day in diet.

Classification: core-GUIDELINE. The study satisfies the requirement for an 83-2 oncogenicity study in mice.

(45)

Special Review Criteria (40 CFR 154.7): Study demonstrates apparent compound related increases in liver adenomas.

A Quality assurance statement was signed by Margery J. Wirth and dated June 13, 1991.

A Good Laboratory Practices statement was provided.

A. MATERIALS and STUDY CONSTANTS:

1. Test material: MGK[R] 264 (N-octyl bicycloheptene dicarboximide). From lot #3843. The material was described as a viscous pale yellow liquid and was provided by the McLaughlin Gormley King Company, Minneapolis, Minnesota.

Stated as being of 98% purity and containing 2% inerts. Appendix B of the study report reported the results of the sponsors (MGK Company) analysis of the test article. This report indicated that two samplings (one each on Nov 25, 1987 and May 26, 1988) had purities of 92.4 and 92.8% respectively. No information on the chemical composition of the inerts or contaminants was provided. Note: The study report states that three samples were analyzed by the sponsor, but Appendix B reports the results of only two.

2. Test animals: **Species:** Mouse; Strain: Charles River CD-1[R]; **Age:** 28 days old on arrival and approximately 48 days (7 weeks) at start of dosing following a 20 day acclimatization period; **Weight:** males were 21 to 31 gms and females were 18 to 27 gms prior to initiation on their diets; **Source:** Charles River Breeding Laboratories, Inc., Portage, Michigan (received November 13, 1986).

B. STUDY DESIGN:

1. Animal assignment

Animals were reportedly assigned to their dosing groups by means of a computer assisted randomization procedure which employed Bartlett's Chi-square test for homogeneity of variance as follows:

Dosage Level[1] mg/kg/day	Number of Mice Males	Females
Control A	50	50
Control B	50	50
50	50	50
400	50	50
800	50	50

[1] The diets were prepared periodically (weekly) based on body weights and food consumption to give the dose levels in mg/kg/day as indicated.

There were no satellite groups for interim sacrifice included. The mice were individually housed during treatment.

2. Diet preparation

Diet was reportedly prepared weekly and presented to the animals (any storage was thus for one week at room temperature). Homogeneity, stability and concentration were assessed as follows.

i. Homogeneity. The results of a single study were presented (Appendix F of the study report). Ten 50 gram samples were taken from stratified layers of each diet preparation following the blending intervals. The mean (range) in percent for these analyses were 94 ± 11.4 (77-108), 106 ± 8.9 (89-118), 98 ± 3.0 (92-101) and 98 ± 2.4% (95-102) for the low (blendings for 10 and 20 mins), mid and high dose groups respectively based on target concentrations of 234, 2,286 and 5840 ppm. These data indicate acceptable homogeneity.

ii. Stability. The stability of MGK 264 stored at room temperature for ten days in the test diets prepared at 234, 2,286 and 5,840 ppm was determined to be 95, 98 and 98% respectively. These data indicate that only as much as 5% decomposition occurred in the low dose level over the ten day interval based on assays at day 0 and 10.

iii. Concentration. Duplicate samples of both the male and female test diets were assessed for the first four weeks and then for each fourth week thereafter (22 assay intervals were

reportedly assessed). The means for the low dose males and females were both 95% (standard deviations of 4.0 and 2.4 for males and females), The means for the 22 determinations for the mid and high dose groups were 97 or 98% (with standard deviations of 2.2 to 2.9%). These data indicate acceptable attainment of the test article concentration in the diet.

3. Animals received food (Certified Purina Rodent Chow #5002) and water ad libitum.

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

Statistical Tests	Parameters Investigated
Analysis of Variance (one way classification); Bartlett's tests for homogeneity; t-statistics for equal or unequal variance; and Dunnett's multiple comparison tables	body weights food consumption hematology absolute and relative organ weight [All tests were two-tailed with $p < 0.05$ and $p < 0.01$ used as levels of significance.
Huff statistical procedure including life table test; Hoel-Walbury "incidental tumor" test; Fisher's Exact test; and Cochran-Armitage trend test	Tumor data.

C. METHODS AND RESULTS:

1. Clinical signs/observations. Animals were reportedly inspected three times daily on weekdays and twice daily on weekends and holidays for signs of toxicity and mortality. More detailed examinations were reportedly made weekly.

Clinical signs of toxicity. No evidence of compound related toxicity or clinical signs were reported.

Mortality (survival). Survival between treated and each of the control groups was reported as being comparable. There were 41, 37, 41, 36, 32 males and 39, 33, 47, 35 and 34 females reported surviving to weeks 79/80 for the control (two groups), low, mid and high dose groups respectively. Since there were 50 mice/sex in each dose group, there was > 50% survival for all groups indicating reasonably good care of the mice during the study.

NOEL (clinical signs and survival) > 800 mg/kg/day (HDT).

[Note: There were only 32 high dose group males surviving as compared to 41 and 37 control males for two groups. This implies a possible compound related decrease in survival but this could not be supported by either symptoms, body weight change or statistics. The increase in male deaths was not due to liver tumors because all 12 tumors were in the survivors (see below).]

2. Body weight. Individual mice were reportedly weighed at pretest and weekly for the first 16 weeks, then for every four weeks until week 78. The study author maintains that the body weight differences were "not toxicologically significant". Table 1 illustrates the mean body weights at selected intervals for both males and females.

Table 1. Mean body weight for males and females at selected intervals.

Week		Dose Level (mg/kg/day)[1] Control A	Control B	50	400	800
-1	M	29/1.9	26/1.9	26/2.0* (-3.7%)	26/1.9	26/1.9
	F	23/1.3	23/1.4	22/1.5	23/1.0	22/1.6
4	M	31/2.3	30/2.2	30/2.6	30/2.3 (-3.3%) ns	30/2.3
	F	26/1.8	26/1.7	26/1.7	26/1.6	26/2.1
13	M	35/2.9	34/2.7	34/3.5	33/2.6** (-5.7%)	33/2.5* (-5.7%)
	F	29/2.4	29/2.3	30/2.3	29/2.3	29/2.3
28	M	37/3.7	37/3.6	36/4.3	36/2.9* (-2.7%)	36/2.7* (-2.7%)
	F	31/2.3	31/2.5	31/2.9	31/2.9	30/2.4
52	M	38/4.4	38/4.3	37/3.8	36/3.0** (-5.3%)	36/3.0** (-5.3%)
	F	34/2.9	35/3.3	33/2.9	33/3.0* (-5.7%)	32/2.5** (-8.6%)
78	M	38/3.5	38/4.3	37/3.9	35/3.2** (-7.9%)	36/2.6 (-5.3%)
	F	36/3.4	37/4.4	36/3.9	35/5.3	34/2.6** (-8.1%)

* $p < 0.05$, ** $p < 0.01$, ns = not significant when compared with the controls (usually the decrease was significant when compared to the higher of the two controls but occasionally it was significant when compared with both controls.

1. The data are presented as mean body weight/standard deviation of the mean. Where the weight was noticeable or statistically different the percent difference is in parenthesis. The number of animals weighed varied as the study progressed due to decedents.

Body weight gain data were not calculated since the differences in absolute body weight were either nonexistent or very small (about 1 to 2 grams) from weeks 1 to 28 when the mice

were considered fully grown and had gained about 11 grams. Thus, there was no overt effect on growth.

Male body weight for the mid dose group was significantly lower (about 2 to 8%) almost at every interval after week 2 when compared with the higher control group. For only about half of the weighings, however, it was lower when compared to both control groups. The high dose male group, however, was statistically significant for about one third of the weighings, with the interval between week 20 nd 60 being significantly lower (about 2 to about 6%). Final body weight was about 8% lower for the mid dose group ($p < 0.01$) and about 5% (not significant) for the high dose group.

Female body weight was rarely significantly decreased in the mid dose group (on only four occasions out all 32 intervals). Female high dose group was significantly decreased almost always after the week 32 until termination when compared with control group B. After week 60, it was significantly decreased relative to both control groups.

Body weight decreases were less than 10%. The mid and high dose group appear to be marginally affected but a definite conclusion for a compound related decrease in weight is obscured because comparison with both controls groups did not reach statistical significance and there is not a clear dose-response between 400 and 800 mg/kg. An effect on body weight for the higher dose groups may be obscured because of concurrent increases in liver weight in these groups.

3. Food consumption and compound intake.

Food consumption was reportedly determined at pretest and weekly for the first 16 weeks, then for every four weeks until week 78.

The study report asserts that although food consumption in gm/kg/day was frequently decreased for all dose groups, the effect is not toxicologically significant. When expressed as gm/animal/day these decreases ranged from about 2.0% to about 3.9% for males with the mid and high dose group being about 3.9% decreased when compared to either control group. For females the decrease was about 1.8% to 5.4%. The mid dose group was about 5.4% decreased but the high dose group was about 3.6% decreased.

Compound Intake was reportedly determined by comparing the weight of the mice with the food consumed. Compound intake was 49.52, 396.08 and 787.86 mg/kg/day for males and 49.41, 397.25 and 789.57 mg/kg/day for females for the low, mid and high

dose groups. These values are very close to the target dose levels of 50, 400 and 800 mg/kg/day.

NOEL (body weight and food consumption). None assigned. No effect at 50 mg/kg/day but small decreases in body weight may be obscured by increases in liver weight for the 400 and 800 mg/kg/day groups. See Table 2 below.

4. Ophthalmological examinations. Reportedly performed on all mice at pretest and at week 76. The mice were reportedly examined with a binocular indirect ophthalmoscope following pupillary dilation with 1% tropicamide. Additional details of the ophthalmoscopic examination were described in the methods section.

Notations for the pretest and week 76 examinations were presented in Appendix M of the study report. There were no compound related increases in ocular lesions noted by ophthalmoscopy.

5. Blood analysis. Blood was collected at 12 and 18 months from 10 mice/sex.

a. Hematology. Table 8 of the study report (p. 183) presented evidence that the following parameters were investigated:

leukocytes	erythrocytes
hemoglobin	hematocrit
mean cell volume	mean cell hemoglobin
mean cell hemoglobin concentration	platelets
segmented neutrophils	lymphocytes

No compound related effects were evident. Only occasional deviations were noted.

NOEL (hematology) > 800 mg/kg/day.

b. Clinical Chemistry and Urinalysis. No determinations made.

7. **Organ weight.** Evidence (Table 10 page 208 of the study report) indicated that the following organs were weighted: adrenals (left and right), brain (with stem), heart, kidney (left

and right), liver (with gall bladder), ovary (left and right), spleen and testes (left and right). Data on absolute weight and relative to body and brain were presented.

Table 2 below illustrates the liver weight (absolute, and relative to body weight) to indicate possible compound related changes in this organ. Liver weight relative to brain weights were also determined and the results were qualitatively similar to liver weight relative to body weight.

Table 2. Liver weight analysis.

Group	Control A	Control B	50 mg/kg	400 mg/kg	800 mg/kg
	Dose Level (Group Mean/Stand. Dev.)				
Males N[1]	39	37	39	36	30
Absolute	1.77/0.3	1.84/0.36	1.76/0.36	2.04/0.41	2.48/.41
%[2]	--	--	--	+12.7%**	+37.0%**
Relative	5.33/0.87	5.68/1.08	5.49/1.02	6.71/1.17	8.02/1.45
%	--	--	--	+21.8%**	+45.6%**
Females N	39	33	46	35	34
Absolute	1.75/0.27	1.78/0.31	1.77/0.32	1.91/0.30	1.87/0.25
%	--	--	--	+8.2%	+5.9%
Relative	5.69/0.72	5.61/0.82	5.76/0.86	6.28/0.85	6.55/0.80
%	--	--	+1.9%	+11.2%**	+15.9%**

** Statistically significant ($p < 0.01$) different from one (the highest) or the other or both of the control groups. Study report statistics.
1. Number of mouse livers weighed.
2. The percent effect relative to the control groups was determined by the reviewer comparing the value for each dosed group with the mean for the control groups.

The above table indicates that liver weight both absolute and relative to body weight were significantly increased for the males in both the mid and high dose groups. Only relative liver weight in the mid and high dose groups was significantly elevated for females although absolute weights for both the mid (8.2%) and high (5.9%) were slightly elevated. The increases in liver weight at 400 and 800 mg/kg/day and the observation that males are more affected than females is consistent with the results of the range finding study (see Appendix I).

Other organs showing some significant differences from

the controls were the brain, adrenal and heart for males but these were in the 400 mg/kg/day dose group only and the brain and kidney for females (both in the 800 ppm dose group). These organs weight differences were not considered to be definitely directly related to the test material.

NOEL/LEL (organ weights) = 50/400 mg/kg/day. At 400 mg/kg/day and above absolute and relative liver weight increases in both sexes.

7. **Pathology-Individual Organ Discussions.**

Inspection of Table 11 of the study report indicated that the following organs/tissues were examined:

Adrenal (cortex and medulla), aorta, bone (femur and tibia), bone marrow (femur), brain, cecum, colon, duodenum, epididymis, esophagus, eye (and optic nerve), gallbladder, Harderian gland, heart, hemolymphatic reticular system, ileum, jejunum, kidney, lacrimal gland, liver, lung, lymph node (axillary, inguinal, mandibular, mesenteric, mediastinal, regional, submandibular), mammary region (females only), nerve (sciatic), ovary, pancreas, parathyroid, penis, pituitary, prepuce, preputial gland, prostate, rectum, salivary gland, seminal vesicle, skeletal muscle, skin (ear, eyelid) , soft tissue (head, tail, abdomen and foot), spinal cord (cervical, lumbar and thoracic), spleen, stomach (glandular and non-glandular), testis, thymic region, thyroid, trachea, ureter, urinary bladder and uterus (and cervix) and vagina.

The survivors (and moribund mice) were sacrificed by carbon dioxide asphyxiation and subjected to gross necropsy. The methods section states that "a full compliment of the listed organs tissues were collected from both control and high dose groups and those animals died or sacrificed in extremis. Only selected organs (liver, lungs, kidneys and gallbladder) as well as tissue masses and regional lymph nodes and gross lesions were examined from the low and mid dose groups. Only standard methods were used for tissue preparation for micropsy. No special stains were employed.

The pathology report did not include statistical analysis of the lesions presented except for selected liver and lung lesions.

The following is an individual organ analysis of the data presented.

A. Liver and gallbladder. The liver was indicated in the study report as a target organ for neoplastic and non-neoplastic effects of MGK-264 administration. Liver weight was increased at 400 mg/kg/day and above. Gross necropsy revealed increases in liver "masses" and "nodules". There 5, 6, 5, 7 ad 10 incidents of masses males and 4 8, 6 13 and 15 incidents of "nodules" for the males control to high dose groups respectively. There were only 2 incidents of "masses" but 2, 2, 1, 2 and 6 incidents of "nodules" among the females for the control to high dose groups respectively.

Table 3 illustrates the liver histopathology findings.

Table 3. Compound related gross and histopathological findings in the liver and gallbladder of male and female mice.

Lesion		Dose Level (mg/kg/day)[1] Control A	Control B	50	400	800
Non-neoplastic pathology						
Gall bladder: Single or multiple biliary calculi ("calculus")	M	0/47	2/46	0/45	11/48	19/49
	F	0/43	0/49	0/47	3/49	9/50
Liver: Intrahepatic bile stasis	M	0/49	0	0	5	45
Hepatocellular hypertrophy	M	2/49	3	1	2	30
	F	0/48	0	0	0	6
Neoplastic- Males						
Hepatocellular adenoma		3*	1	1	6 (0.056)	12*/**
Carcinoma		0	2	1	3	1
Total		3*	3	2	9 (0.061)	13**/**
-Females						
Hepatocellular adenoma		0 (0.059)	0 (0.059)	0	1	2
Carcinoma		0	0	0	0	1
Total		0	0	0	1	3 (0.121)

1. The denominator is the number of animals examined. If there is no denominator, 50 animals were reportedly examined.

* On control data indicates the trend is significant ($p < 0.000$) by the Cochran Armnitage trend test. Study report statistics[1].

* or ** on data for the high dose group indicates the pair wise comparison by Fisher's Exact test is significant. The * above the / is the result of comparison with control group A, below the / comparison with control group B. Study report statistics.

The p value is given in () when the data nearly reached statistical significance.

[1] Note: HED will do additional statistics based on animals at risk prior to the HED Carcinogenicity Peer Review meeting. The above statistics did not eliminate animals which were too autolyzed for diagnosis.

Historical control (p. 1456) data from 6 studies (including 11 separate control groups of 50 to 120 mice/sex) were provided in the study report for the occurrence of liver nodules, hepatocellular adenomas and carcinomas. These data are appended. In summary, the spontaneous occurrence of liver tumors in the controls is as follows:

Hepatocellular Adenoma:

Males: Range 0-18.33% per control group or 74 incidents out of 745 animals (9.93)%.
Females: Range 0-3.33% per control group or 7 incidents out of 745 animals (0.94%)

Hepatocellular Carcinoma:

Males: Range 0-5.0% per control group or 17 incidents out of 745 animals (2.3%).
Females: Range 0-1.67% per control group or 1 incident outof 745 animals (0.13%).

Other liver lesions. In addition to the lesions indicated in Table 3 above the following lesions were reported and were considered to be compound related in the high dose group only

-Biliary calculi in large intrahepatic bile duct (reported in Table 11 of the study report as "calculus".

In males there were 9 animals affected in the high dose group (5 survivors), 0 in all other groups.

In females there were 2 animals affected in the high dose group, 0 in all other groups.

-Portal bile duct proliferation.

In males there were 30 animals affected in the high dose group (24 survivors), 0 in all other groups.

There were no animals reported as affected in females.

-Portal mononuclear cell infiltration.

In males there were 13 animals affected in the high dose group (all survivors), 0 in all other groups.

In females one control and one 400 mg/kg/day dose group animal was affected.

-Spongiosis hepatis.

In males there were 4 animals affected in the high dose group (3 survivors), 0 in all other groups.

There were no animals reported as affected in females.

-Hyperplastic nodules.

In males there were 12 mice affected in the high dose group (all survivors), 5-8 in the other groups.

In females there were 3 mice affected in the high dose group (all survivors), 0-1 in the other groups.

-Cysts.

There were four male mice affected (3 survivors), 0 in all the other groups.

-Vacuolar change. There were 4 male mice affected (all survivors), 0-1 in all other groups.

The non-neoplastic lesions were present about equally in both the decedents and the survivors. The liver pathology including tumors were thus not life threatening within the time frame of the study. For example, 5 of the 6 and all 12 of the mice with liver adenomas in the mid and high dose male groups were survivors.

CONCLUSION (liver and gall bladder pathology, systemic effects). NOEL/LEL = 50/400 mg/kg/day. At 400 mg/kg/day there was increased calculi in the gall bladder and intrahepatic bile stasis in males. At 800 mg/kg/day there was an increase in hepatocellular hypertrophy, calculus in bile duct in males and females and portal bile duct proliferation, portal mononuclear cell infiltration, spongiosis hepatis, cysts and vacuolar change in males and hyperplastic nodules in males and females.

The mid and high dose group males were associated with increases in liver adenomas. The mid and high dose group females had adenomas and a carcinoma which did not reach statistical significance but these liver tumors in female CD-1 mice are rare.

B. Brain. Although there was an indication of possible brain weight increase in both sexes. There were no indications of compound related lesions in the brain.

C. Adrenal. There was an indication of possible weight increase in males.

Adrenal data were presented as both cortex and medulla and there was a high background rate of A cell hyperplasia (86%) and brown pigmentation (68%) but there was no indication of increases in incidence in the higher dose levels of treatment in either sex.

D. Heart. There was an indication of possible weight increase in males.

Amyloidosis was reported more frequently in the high dose groups for males (14/50 or 28%) and females (13/50 or 26%) than in any control group (7/50 or 14%, both male group A and female group B). Amyloidosis was also elevated in several of other organs in the high dose group. Because this is a very common condition in older mice, the slight increases noted are not considered definitely or directly compound related. In any case the NOEL/LEL for liver effects will be inclusive of the dose levels for a possible increase in amyloidosis.

Arteritis was also reported more frequently in female hearts in the high dose group (5/50 or 10%) while there was one incident in each of the controls (or 2%). The aorta did not have this condition. TB-I does not consider this finding to be of toxicological significance.

E. Kidney. There was an indication of possible weight decrease in females. The number of incidents of amyloidosis graded as severe appeared to be slightly higher in the male and female mice dosed with 400 and/or 800 ppm groups. The report author (p.43) attributed amyloidosis of the kidney primarily involving the glomeruli as the single most common cause of death (apparently in all groups since deaths were not considered compound related).

Mineralization of the kidney of males was increased in an apparent dose related manner such that 2/50 (4%), 0%, 6/49 (12%), 9/50 (18%) and 10/49 (24%) for the controls to the high dose group were affected. This condition was not reported as being present in females. This condition was described as "trace" in the high dose group for all but one incident and there was one incident of "mild" in both the control and high dose group. Thus the degree of severity did not increase with increase in dose level. TB-I does not consider that the magnitude of severity justifies that regulatory action be based on this observation at this time and its significance is equivocal. In particular the rat and dog chronic feeding study should be assessed for the presence of mineralization in the kidney to help resolve the

equivocal nature of this observation.

9. **DISCUSSION:** Comparison of the study report conclusions with TB-I conclusions.

Study Report	TB-I Assessment or Comment
Clinical Signs: No effects.	Concurs.
Mortality: No effects.	Slightly poorer survival in males but no cause or concurrent toxicity identified. Deaths not related to liver tumors possibly but indefinitely related to other aspects of liver pathology.
Body Weight/Food Consumption: Weight decreases noted in 400 and 800 mg/kg/day but not considered toxicologically significant effects.	No effect on weight gain evident. Body weight decreases of < 10% noted in mid and later weeks. A decrease in body weight in the later weeks of the study may be obscured by concurrent increases in liver weight.
Ophthalmoscopy: No effects.	Concurs.
Hematology: No toxicologically significant effects.	Concurs.
Clinical Chemistry: No assessments made.	
Organ Weight: NOEL/LEL = 50/400 mg/kg/day. Liver relative weight increased (male and females).	Concurs.
Gross Pathology: NOEL/LEL = 50/400 mg/kg/day. Liver nodules and/or masses said to be limited to males only.	Males affected at 400 mg/kg/day but females have "nodules" at 800 mg/kg/day (see page 10 of DER).

Non-neoplastic Pathology: NOEL/LEL = 50/400 mg/kg/day. At 400 mg/kg/day: calculi in gall-bladder in males and females, in-trahepatic bile stasis in males. 800 mg/kg/day: biliary calculi, hepatocellular hypertrophy, portal bile duct proliferation, portal mononuclear cell infiltration and spongiosis hepatis.	The liver of males was more severely affected than females. Both males and females have hyperplastic nodules at 800 mg/kg/day. Males also have cysts and vacuolar change. The kidney had apparent increases in a dose related manner for mineralization. Only 2% of controls but 20% of high dose males were affected but the degree of severity did not increase with the increase in dose level. Rat and dog chronic feeding studies should be assessed for this condition.
Neoplastic Pathology: Increased hepatocellular adenomas considered compound related at 800 mg/kg/day in males only. Tumors were said to be associated with increase in turnover of hepatocytes and coincident with non-neoplastic liver pathology and the total incidence (24%) is not substantially greater than the historical control (18%).	The combined adenomas and carcinomas in males are statistically significant in the 400 mg/kg/day dose group and the trend is significant for females. Liver tumors are rare in females. Thus the mid dose group males and females may be affected. The classification of MGK-264 will be discussed at the HED Carcinogenicity Peer Review Committee meeting.
Special Assessments: None	
Overall Conclusion for NOEL/LEL: NOEL/LEL = 50/400 mg/kg/day.	Concurs. Refer to non-neoplastic pathology above.
Adequacy of Dosing for Assessing Carcinogenicity:	Only effects in the liver, the organ which also showed carcinogenic effects, were noted. There were no effects on growth (body weight gain) apparent. Dosing at higher levels than the high dose used for this study (800 mg/kg/day) is not considered necessary.

CONCLUSION: This study is CORE GUIDELINE and supports the following "one liner":

NOEL/LEL = 50/400 mg/kg/day. 400 mg/kg/day: Liver weight increases and gall bladder calculi in males and females; and liver/bile duct stasis in males. 800 mg/kg/day: additional liver pathology (biliary calculi, hepatocellular hypertrophy and hyperplastic nodules; in males only: portal bile duct proliferation, portal mononuclear cell infiltration, spongiosis hepatis (degenerative lesion), cysts and vacuolar change.

Liver adenomas males and liver tumors (adenoma and/or carcinoma) present in female dosed animals at 400 and 800 mg/kg/day.

Dose levels tested 0, 50, 400 and 800 mg/kg/day.

Appendix I. Summary of the Dose Range Finding Study.

M. Blair (author) "13 Week Dietary Range-Finding Toxicity Study in Mice with MGK® 264 Insecticide Synergist". International Research and Development Corporation, Study No.: 551-010, October 24, 1991 (date of amended report), Study completion date: February 4, 1987, MRID No.: 420938-01.

The basic design of this study consisted of dosing 6 groups of 10/sex of Charles River CD®-1 mice (Charles River laboratories, Portage, Michigan) with either 0, 125 (4000), 250, 500, 1000 or 2000 mg/kg/day of MGK 264 (Lot No.: 3843, reportedly of 98% purity) incorporated into their diets for 13 weeks. The group dosed with 125 mg/kg/day was switched to 4000 mg/kg/day beginning at week 7. The objective of the study was to obtain toxicity data to help set the dosage levels for the definitive mouse carcinogenicity study.

The results at each test dose level are summarized as follows.

125 mg/kg/day (weeks 1-7 only): No obvious effects during dosing period. No data to assess if liver weight is affected.

250 mg/kg/day: Absolute and relative to body weight liver weight increase in males.

500 mg/kg/day: Relative to body liver weight increase in females. Liver weight increase continuation in males. Male liver weight to brain weight increase.

1000 mg/kg/day: Male and female absolute and relative to body and brain liver weight increases; bile stasis (all males, 4 females), liver hypertrophy (4 males), portal bile duct proliferation (1 male), portal mononuclear cell infiltrate (1 male and female).

2000 mg/kg/day: No animals died. The notable symptoms included decreased defecation (all animals), Among the males there were occasional occurrences of "firm area, abdomen" (1 incident) and dark yellow urine (2); hepatomegaly and dark discolor-ation of the liver (most animals); male and female absolute and relative to body and brain liver weight increases; bile stasis (all males, 9 females), liver hypertrophy (9 males, 7 females), portal bile duct proliferation (9 males, 8 females), portal mononuclear cell infiltrate (10 males, 8 females), cholanglofibrosis (8 males, 7 females)

4000 mg/kg/day (weeks 7-13 only): Two male deaths, one each at weeks 8 and 9 and one female sacrificed moribund at week 11.

Notable clinical signs included "firm area, abdomen", tremors, decreased defecation (all animals), dark yellow urine, anogenital region yellow, reduced motor activity, labored breathing and cold to touch; body weight decrease (-15% males $p < 0.01$, -10% females $p < 0.05$ when compared to control after 13 weeks); decreased food consumption; hepatomegaly and dark discoloration of the liver (most animals); male and female absolute and relative to body and brain liver weight increases.
bile stasis (9 males and 9 females), liver hypertrophy (8 males, 9 females), portal bile duct proliferation (8 males, 9 females), portal mononuclear cell infiltrate (8 males, 9 females), cholanglofibrosis (8 males and 8 females).

Note: Body weight gain data ranged from 5-9 gms for males and 5-7 grams for females for the several dose levels tested. due to the wide range, it is uncertain if the mice dosed with 2000 mg/kg/day actually had decreases in body weight gain. Both the male and female 4000 mg/kg/day groups had an apparent 29% decrease in body weight gain based on both control groups gaining 7 gms and both 4000 mg/kg/day groups gaining only 5 gms.

DISCUSSION. The critical determinants used by the registrant in setting the dose levels for the definitive study were increases in liver weight, decrease in body weight and liver pathology. Liver weight effects were noted at all dose levels for which weight data were available and Table 1 illustrates the effects.

The highest dose level selected for the definitive study was 800 mg/kg/day. According to the demonstration of liver weight effects in both sexes at 500 mg/kg/day and hepatocellular changes at 800 mg/kg/day dose level. Since the low dose of 250 mg/kg/day in this study resulted in increased liver weight in males, the selection of 50 mg/kg/day for the definitive study as the low dose is considered reasonable by TB-I. Since liver effects alone are not always considered adequate or excessive toxicity, TB-I considers that higher doses up yo 2000 mg/kg/day could have been tolerated.

Table 1. Liver weight analysis.

Dose Level mg/kg	Absolute M	Absolute F	Relative to Body M	Relative to Body F	Relative to Brain M	Relative to Brain F
0	1.97/.18	1.82/.28	5.55/.32	5.83/.70	3.94/.75	3.36/.46
125	No data		No data		No data	
250	2.22/.28* (11.7%)	1.82/.15	6.14** (10.6%)	5.95 (2.1%)	4.30 (11.2%)	3.5 (4.2%)
500	2.38/.28** (20.8%)	1.94/.25 (6.6%)	6.80** (24%)	6.45* (10.6%)	4.76* (20.8%)	3.58 (6.5%)
1000	2.66/.25** (35%)	2.19/.26** (20.3%)	7.65** (37.8%)	7.23** (24%)	5.18** (31.5%)	4.18** (23.7%)
2000	3.78/.51** (91.9%)	3.13/.61** (72%)	11.28** (103.2%)	10.41** (78.6%)	7.25** (84%)	6.11** (81.9%)
4000	5.27/.54** (167.5%)	4.28/1.0** (135.2%)	16.39** (195.3%)	14.26** (144.6%)	10.96** (178.2%)	8.59** (155.7%)

Data are gm for the absolute weight but a percent for the relative weights. The denominator when present is the standard deviation, not all standard deviations are presented to clarify the table.
* $p < 0.05$ and ** $p < 0.01$ study report statistics.

International Research and Development Corporation
Historical Control Data - Neoplastic Lesions
18 Month CD-1 Mouse

Study		A	B		C		D		E		F	
Initiation/termination dates		7/02/86-1/08/88	12/05/85-6/29/87	12/05/85-6/29/87	1/27/87-10/05/88	1/27/87-10/05/88	11/21/85-6/01/88	11/21/85-11/25/86	10/06/86-6/09/88	10/06/86-6/09/88	2/02/87-8/09/88	2/02/87-8/09/88
Number of animals initiated		65	60	120	60	120	50	50	60	60	60	60
		Control 2	Control 1	Control 2	Control 1	Control 2	Control A	Control B	Control A	Control B	Control 1	Control 2
MALES												
LIVER		(65)	(60)	(120)	(60)	(120)	(50)	(50)	(50)	(50)	(60)	(60)
Hyperplastic nodule	Inc.	2							3	6	9	4
	% Inc.	3.08							6.00	12.00	15.00	6.67
Hepatocellular adenoma	Inc.	5	7	17	11	18	7		6	1	2	
	% Inc.	7.69	11.67	14.17	18.33	15.00	14.00		12.00	2.00	3.33	
Hepatocellular carcinoma	Inc.		3	3	1	3	1	2		2	1	1
	% Inc.		5.00	2.50	1.67	2.50	2.00	4.00		4.00	1.67	1.67
LUNG		(65)	(60)	(120)	(60)	(120)	(50)	(50)	(50)	(50)	(60)	(60)
Alveolar bronchiolar adenoma	Inc.	10	10	18	4	18					19	8
	% Inc.	15.38	16.67	15.00	6.67	15.00					31.67	13.33
TESTIS		(65)	(60)	(120)	(60)	(120)	(49)	(50)	(50)	(50)	(60)	(60)
Leydig (interstitial) cell tumor, benign	Inc.			1				1			1	
	% Inc.			0.83				2.00			1.67	
FEMALES												
LIVER		(65)	(60)	(120)	(60)	(120)	(50)	(50)	(50)	(50)	(60)	(60)
Hyperplastic nodule	Inc.						2			1	2	
	% Inc.						4.00			2.00	3.33	
Hepatocellular adenoma	Inc.		2	2		1			1		1	
	% Inc.		3.33	1.67		0.83			2.00		1.67	
Hepatocellular carcinoma	Inc.										1	
	% Inc.										1.67	
LUNG		(65)	(60)	(120)	(60)	(120)	(50)	(50)	(50)	(50)	(60)	(60)
Alveolar bronchiolar adenoma	Inc.	9	13	12	4	8					10	19
	% Inc.	13.85	21.67	10	6.67	6.67					16.67	31.67

( ) = Number of animals examined microscopically
Inc. - Incidence
% Inc. - percent incidence

551-011

IRDC

1457

66

MRID 420938-02
Study # 551-011

83-2 Oncogenicity in Rats or Mice

ACCEPTANCE CRITERIA

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 50 animals/sex/group (3 test groups and control group).
3. ✓ Dosing duration is at least 18 months for mice and 24 months for rats.
4. ✓ Number of survivors in any group does not fall below 50% at 15 months for mice, 18 months for rats or 25% at 18 months for mice, 24 months for rats.
5. ‡ A Doses tested include an MTD or limit dose if nontoxic (1,000 mg/kg).
6. * ✓ Doses tested include a NOEL for systematic effects.
7. * ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
8. ✓ Individual daily observations.
9. ✓ Individual body weights.
10. ✓ Individual or cage food consumption.
11. ✓ Individual necropsy of all animals.
12. B Blood smear from 10 animals/sex/dose at 12 and 18 months and termination. Differential count high dose and controls, all other doses if high dose shows pathology.
13. ✓ Histopathology of the following tissues performed on all interim sacrifice animals, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

✓ aorta	✓ jejunum	✓ peripheral nerve
✓ eyes	✓ bone marrow	✓ kidneys†
✓ caecum	✓ liver†	✓ esophagus
✓ colon	✓ lung†	✓ ovaries†
✓ duodenum	✓ lymph nodes	NO oviduct not specifically
✓ brain†	✓ stomach	✓ pancreas
✓ skin	✓ mammary gland	✓ rectum
✓ heart†	✓ spleen†	✓ spinal cord (3x)
✓ testes†	✓ musculature	✓ thyroid / parathyroids
✓ pituitary	✓ epididymis	✓ salivary glands
✓ ileum	✓ adrenals†	✓ thymus
✓ trachea	✓ uterus	✓ urinary bladder

† organs to be weighed

‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncogenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review, may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and

Criteria marked with a * are supplemental and may not be required for every study.

A=

B= hematology assessment made

considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

Criteria marked with a * are supplemental and may not be required for every study.

ATTACHMENT 5

. . . . . Free Standing Toxicity Summary

Toxicity Data Base: MGK-264 Tox Chem No.: 613
PC Number:

Series. Study Type	Executive Summary
81-1. Acute Oral Toxicity	No Study
81-2. Acute Dermal Toxicity	No Study
81-3. Acute inhalation Toxicity	No Study
81-4. Primary Ocular Irritation	No Study
81-5. Primary Dermal Irritation	No Study
81-6. Dermal Sensitization	No Study
81-7. Delayed Type Neurotoxicity	Study not required
81-8. Acute Neurotoxicity Screen	Basis for requiring study needs review
82-1a. Subchronic Feeding - rat IRDC Study No.: 551-028, August 9, 1989. MRID No.: 429706-01 Classification: SUPPLEMENTARY HED Document No.: 011100	No separate DER prepared. Refer to 83-5.
82-1b. Subchronic Feeding - nonrodent	No Study. Refer to 83-1b
82-2. 21-Day Dermal	No Study.
82-3. 90-Day Dermal Toxicolo Laboratories, England Study No.: MCA/17/92 March 19, 1993 MRID No.: 427422-01 Classification: MINIMUM HED Document No.: 010573	New Zealand White rabbits were dosed with 0, 10, 30 or 100 mg/kg/day of MGK-264 (lot 3843, 92% purity) in corn oil for seven days/week for 13 weeks. No systemic reactions to treatment were evident. Local site of application dermal reactions were noted at <u>all</u> dose levels due to the vehicle.
82-4. 21 or 90 Day Inhalation Pharmac::LSR Study No.: 91-8364, June 14, 1994 MRID No.: 433090-01 (3 volumes) Classification: HED Document No.:	[Under review as of 11/94]
82-5. 90-day neurotoxicity (old version).	Study not required.
82-7. 90-day neurotoxicity screen.	Basis for requiring study needs review
83-1a. Chronic Feeding - rat	Refer to 83-5.

83-1b. Chronic Feeding -nonrodent IRDC Study No.: 551-031, December 16, 1991 MRID No.; 421481-02 Classification" GUIDELINE HED Document No.: 010107	Beagle Dogs were dosed with 0, 65, 250 and 1000 ppm corresponding to 0, 2.1, 7.5 and 33.7 mg/kg/day of MGK-264 (92.6%, lot 7437) for one year. At 33.7 mg/kg/day liver effects described as brown pigment disposition in both sexes and hepatocellular hypertrophy in males resulted. **The LEL is 33.7 mg/kg/day based on liver effects. The NOEL is 7.5 mg/kg/day.**
83-2. Oncogenicity-mice IRDC Study No.: 551-011, June 13, 1991 MRID No.: 420938-02 Classification: GUIDELINE HED Document No.: 009273	Charles River CD-1 strain mice were dosed with 0, 50, 400 and 800 mg/kg/day MGK-264 94.2%) for 2 years. Compound related increase in <u>liver tumors (adenomas) in males</u> at 400 and 800 mg/kg/day and also equivocal increase in females. Systemic toxicity included liver and gallbladder calculi in males and females, liver bile duct stasis in males at 400 mg/kg and above. At 800 mg/kg/day: additional liver pathology (bililary calculi, hepatocellular hypertrophy and hyperplastic nodules in males and females, in males only: portal bile duct proliferation, portal mononuclear cell infiltration, spongiosis hepatic (degenerative lesion),-cysts and vacuolar change. **The LEL is 400 mg/kg/day based on liver pathology. The NOEL is 50 mg/kg/day.**
83-3a. Developmental Toxicity - rat IRDC, Study No.: ???, March 1976 MRID No.: Classification: MINIMUM HED Document No.: 003931	<u>Strain</u> rats were dosed with 0, 40, 200 or 1000 mg/kg/day during days 5-15 of gestation. <u>Maternal toxicity</u> was evident by decreased weight at 1000 mg/kg. **LEL for maternal toxicity = 1000 mg/kg/day. NOEL = 200 mg/kg/day.** Developmental toxicity was evident at 200 mg/kg/day by increased resorptions and increased index of variants. No teratogenic effects were noted. **LEL for developmental toxicity = 200 mg/kg/day based on resorptions and variants. NOEL = 40 mg/kg/day.**
83-3b. Developmental Toxicity - rabbit	No study.
83-4. Multi generation reproduction - rat IRDC Study No.: 551-027, December 18, 1991 MRID No.: 421551-01 Classification MINIMUM HED Document No.: 009791	Sprague-Dawley strain rats were dosed with 0, 1250, 1500 or 10000 ppm equivalent to 0, 60.9, 124.9 or 649.3 mg/kg/day in males and 0, 72.5, 150.5 or 759 mg/kg/day in females. <u>Hepatocellular hypertrophy</u> in parental generations and decreased body weight during lactation resulted at 1250 ppm. Decreased body weight and food consumption resulted in adults at 1500 ppm. **LEL < 1250 ppm** based primarily on hepatocellular hypertrophy and decreased body weight during lactation. **No NOEL established.**

83-5. Combined chronic feeding/carcinogenicity IRDC Study No.: 551-030, October 8, 1993. MRID No.: 430053-01 (7 volumes) Classification: MINIMUM HED Document No.: 011100	Five groups of 60/sex Charles River CD[R] strain rats were dosed as either control (two separate groups), 50, 150 or 450 mg/kg bw/day of MGK-264 in their diets in a study designed to assess for chronic feeding toxicity and carcinogenicity effects. The 50 mg/kg/day group males had marginally increased (14% $p < 0.05$) terminal liver weight and higher dose levels had higher increases (maximum 45% for the high dose male and 59% for the female groups. At dose levels of 150 and above pathological changes in the liver (hepatocyte hypertrophy in both sexes and portal bile duct proliferation and bile stasis, spongiosis hepatitis and cysts in females) and kidney (brown pigment in females). At 450 mg/kg: additional liver pathology (bile duct proliferation, cysts and altered eosinophilic foci in males and spongiosis hepatitis in males) and kidney (brown pigment and cysts in males); kidney, heart and brain weights were increased. Several parameters were noted to be highest in the high dose test group especially for males but their association with treatment was indefinite (see DER for list). **The systemic LEL is 150 mg/kg based on increased liver weight supported by liver pathology (i.e. hepatocyte hypertrophy). The NOEL is 50 mg/kg/day.** The study did not indicate carcinogenic potential except for increased thyroid follicular tumors in males which indicated a response of 2, 1, 4, 5 and 6 for adenomas alone and 4, 1, 6, 7 and 9 for combined adenomas and carcinomas for the two control, low mid and high dose animals respectively (based on 60 per dose group). The issue of possible carcinogenicity based on thyroid data will be reviewed further by HED's Carcinogenicity Peer Review Committee.
84-2. Mutagenicity/genetic toxicity Ames test Hazleton, Study No.: 14413-0-401R, August 28, 1991 MRID No.: 420045-02 Classification: ACCEPTABLE HED Document No.: 009789 ..... Chromosome aberrations ..... Unscheduled DNA synthesis	No evidence of mutagenicity in *Salmonella typhimurium* strains TA1535, TA1537, TA1538 or TA100 in presence or absence of metabolic activity. Dose levels tested: 100, 333. 337, 1000 or 3330 ug/plate (no cytotoxicity noted). ..... No acceptable study. .....
85-1. General Metabolism Biol. Testing Center Irvine Calif. Study No.: PO1930 & PO1933, April 30, 1990 MRID No.: 427297-01 to 06. Classification: MINIMUM HED Document No.: 010583	Absorption, retention and metabolite identification assessed in rats using [hexyl-1-^{14}C] or [norbornene-2,3-^{14}C]MGK-264. Refer to review for results.

85-2. Dermal Penetration.	

Special Toxicology Issues and Problems

1. **Labelling.** There are insufficient acute toxicity data to define special labelling requirements based on the characteristic toxicity of the active ingredient. There is no series 81-6 dermal sensitization study with MGK-264. The labelling of the formulations should be governed by the individual acute toxicity studies with each formulation.

2. **Carcinogenicity.** The mouse carcinogenicity study revealed compound related increases in liver tumors (adenomas) in the mid and high dose group males.

The rat carcinogenicity raised the question of possible compound related thyroid tumors (adenomas) in both sexes.

As of November 1994, MGK-264 needs to be reviewed by the HED Carcinogenicity Peer Review Committee for classification for carcinogenicity.

3. **RfD.** MGK-264 does not have an RfD assigned by HED or EPA. The toxicity data base will be presented to the RfD committee in early 1995.

4. **Non-carcinogenic risk assessments.** MGK-264 is an inhibitor of the cytochrome oxidase liver (and possibly other organs cites) detoxification system. Such inhibition may pose special problems not included in establishing the RfD for this chemical. For example, if the exposure to MGK-264 is sufficient to inhibit the cytochrome oxidase then natural alkaloids in foodstuffs may not be detoxified at a sufficient rate such that toxic levels of alkaloids occur in the systemic circulation with potential for concurrent systemic toxicity. The inhibited cytochrome oxidase may also interfere with drugs a person takes since drugs often need to be metabolized to their active form to be effective or they are detoxified by the liver so that toxic levels are not attained in the body. The inhibited cytochrome oxidase system would thus compromise drug actions and reactions. Lastly, the human infant does not have a fully developed cytochrome oxidase system, thus exposure to infants to inhibitory dose levels of MGK-264 would be further compounded in infants.

5. **Mutagenicity/genetic toxicity.** Acceptable studies demonstrating lack of mutagenicity/genetic toxicity are available for bacteria mutagenicity (Ames test) and unscheduled DNA synthesis. There is no study for chromosome aberrations that meets current standards for acceptability.

6. **Dermal Absorption.** Needs write up!

MGK-2-4

ATTACHMENT G

NON-ACUTE TOX PROFILE FOR: N-Octyl bicycloheptenedicarboximide

TOX NO. - 613

STUDY	SPECIES	YR	GR	SYS NEL	SYS LEL	ONCO NEL	ONCO LEL	MAT NEL	MAT LEL	REPROD/ DEV NEL	REPROD/ DEVLEL	MUTA
Developmental Toxicity Study	rat	76				N/A	N/A	200 mg/kg	1000 mg/kg	> 1000 mg/kg		N/A
Multigeneration reproduction	rat	91	M	?	1250 ppm	N/A	N/A					N/A
Carcinogenic	mice	91	G	50 mg/kg	400 mg/kg	? mg/kg	400 mg/kg	N/A	N/A	N/A	N/A	N/A
Feeding-1 year	dog	91	G	8.5 mg/kg	34.7 mg/kg			N/A	N/A	N/A	N/A	N/A
Inhalation-3 month	mice	75		> 4000 mg/kg		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mutagenic-Ames	salmone	86	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	--
Mutagenic-Ames	salmone	91	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	--
Mutagenic-chromosome aberr.	CHO cel	87	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-
Mutagenic-DNA damage/repair	prim cu	87	U	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-
Mut- Chrom. aberr. in vitro	CHO cel	91	U	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Mutagenic-forward mutation	Mamm ce	86	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	?
Mutagenic-unscheduled DNA synt	rat hep	90	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-
Mutagenic-unscheduled DNA synt	rat hep	91	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-
Metabolism	rat	90	M									
Metabolism - dermal absorption	rat	92	A									
Metabolism - dermal absorption	rat	92	A									
Metabolism - dermal absorption	humans	92	A									
Metabolism - dermal absorption	human	92	A									
Dom. animal safety env. exp.	dogs &	90	U									
Dom. animal safety env. exp.	cat (ki	91	A									
Dom. animal safety env. exp.	cat (ki	92	U									

NON-ACUTE TOX PROFILE FOR: N-Octyl bicycloheptenedicarboximide

TOX NO. - 613

STUDY	SPECIES	YR	GR	SYS NEL	SYS LEL	ONCO NEL	ONCO LEL	MAT NEL	MAT LEL	REPROD/ DEV NEL	REPROD/ DEVLEL	MUTA
Dom. animal safety env. exp.	dog (pu	92	U									
Dom. animal safety env. exp.	dog	89	A									
Dom. animal safety env. exp.	cat (ki	92	U									
Dom. animal safety env. exp.	dog (pu	92	U									

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CASWELL#: 613
CAS-REG#: 113-48-4

P.C. CODE 057001- N-Octyl bicycloheptenedicarboximide FILE LAST PRINTED: 11/14/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-2(b) Carcinogenic Species: mice Interntl. Res. and Develop. Co 551-011; 06/13/91	MGK-264 Tech., 92.4-92.8%	420938-02	NOEL/LOEL = 50/400 mg/kg/d. Liver weight increases & gall bladder calculi in males & females; and liver/bile duct stasis in males. 800 mg/kg/d - additional liver pathology (biliary calculi, hepatocellular hypertrophy and hyperplastic nodules in males & females; in males only = portal bile duct proliferation, portal mononuclear cell infiltration, spongiosis hepatic (degenerative lesion), cysts and vacuolar change. Adenomas increased in 400 & 800 mg/kg/day males & liver tumors present in females. Charles River CD-1 mice. Doses: 0, 50, 400 & 800 mg/kg/day (conc. changed to keep dose constant).		Guideline 009273
83-1(b) Feeding-1 year Species: dog Interntl. Res. and Develop. Co 551-031; 12/16/91	MKG-264, 92.6%; lot 7437	421481-02	NOEL/LOEL = 7.5/33.7 mg/kg/day. At 33.7 mg/kg/d: liver effects: (brown pigment deposition in both sexes & hepatocellular hypertrophy in males). Dose levels tested: 0, 65, 250 & 1000 ppm corresponding to: 0, 2.1, 7.5 33.7 mg/kg for both sexes. Species tested: beagle dogs.		Guideline 010107
83-3(a) Developmental Toxicity Study Species: rat International Bioresearch Inc. 3/76	MKG-264 tech		Teratogenic NOEL > 1000 mg/kg. Reproduction NOEL = 40 mg/kg Reproduction LEL = 200 mg/kg (increased resorptions, increased index of variants). Maternal NOEL = 200 mg/kg Maternal LEL = 1000 mg/kg (decreased weight gain) Levels tested = 40, 200, 1000 mg/kg during days 5 - 15 of gestation		003931
83-4 Multigeneration reproduction Species: rat Interntl. Res. and Develop. Co 551-027; 12/18/91	MGK-264 tech. 100%, lot 7437	421551-01	NOEL < 1250 ppm. Hepatocellular hypertrophy in parental generations and decreased body weight during lactation. ≥2500 ppm: Decreased body weight and food consumption in adults. Dose levels tested: 0, 1250, 1500, and 10,000 ppm, equivalent to: 0, 60.9 124.9 and 649.3 mg/kg/day in males and 0, 72.5, 150.5 and 759 mg/kg/day for females based on premating for the F1 parental group. Strain- Sprague dawley (COBS(CD) rat.		Minimum 009791
82-4 Inhalation-3 month Species: mice IBT 663-06080; 8/29/75	MGK-264 5%; Pyrethrins 1% Pip. butoxide 10%; Petr. Dist 4%; [redacted]		NOEL > 40.0 g/hr. (HDT) Levels tested = 0.4 g, 40.0 g per hour, 6 hours/day, 5 days per week for 13 weeks.		003930
84-2(a) Mutagenic-Ames Species: salmonella Microbiological Associates T5205501014; 9/16/86	MGK-264 (purity unspec.) Lot 3843	403991-01	Negative in presence and absence of activation for induced reversions up to toxic doses (333-1000 ug no M.A.; 3333-10,000 ug with M.A.)		Acceptable 006674

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-2(a) Mutagenic-Ames Species: salmonella Hazleton 14413-0-401R; 08/28/91	MGK-264 (FEP-100 Task Force II, Blend 90.78% purity	420045-02	No evidence of mutagenicity in Salmonella typh. strains TA1535, TA1537, TA1538, TA98 or TA100 in presence or absence of metabolic activ. Dose levels tested: 100, 333, 667, 1000 & 3330 ug/plate (no cyto-toxicity noted).		Acceptable 009789
84-2(b) Mutagenic-chromosome aberr. Species: CHO cells Microbiological Associates T5205.337001; 1/14/87	MGK-264 (purity unspec.) Lot 3843	403991-02	Reportedly negative for chromosome activity, but major deficiencies in procedure. [Further data and information satisfied deficiencies].		Unacceptable 006674 Acceptable 007899
84-2(b) Mutagenic-DNA damage/repair Species: prim cult. (HPC/UDS) Microbiological Associates T5205.380009; 4/20/87	MGK-264 (purity unspec.) Lot 3843	403991-03	Reportedly negative for unscheduled DNA synthesis (UDS) in a single assay. But insufficient dosage.		Unacceptable 006674
84-2(b) Mut- Chrom. aberr. in vitro Species: CHO cells Hazleton 14413-0-437C; 08/28/91	MGK-264 (FEP-100 Task Force II, Blend 90.78% purity	420045-01	Study was run with plastic vessels to be repeated in glass vessels to prevent reaction products with piperonyl butoxicde and plastic. Study shows 'severe cytotoxicity' & a possible weak clastogenic effect.		Unacceptable 009789
84-4 Mutagenic-forward mutation Species: Mamm cell (L5178Y/TK Microbiological Associates T5205.701020; 12/15/86	MGK-264 (purity unspec.) Lot 3843	403991-04	Weak positive at toxic doses (0.013-0.018 ul/ml). Cell growth < 20%, test negative with activation.		Acceptable 006674
84-4 Mutagenic-unscheduled DNA synt Species: rat hepatocytes Microbiological Associates T 5205.380026; 11/7/90	MGK 264 insecticide synergist, tech., 93.1%	417032-01	Did not cause unscheduled DNA repair synthesis over a dose range of 0, 0.001, 0.003, 0.01, 0.02, 0.03 uL/mL. Higher doses (to 0.1 uL/mL) too cytotoxic to assay for UDS. Study not a part of Guideline requirements for mutagenicity.		Acceptable 008471
84-4 Mutagenic-unscheduled DNA synt Species: rat hepatocytes Hazleton 14413-0-447R; 08/28/91	MGK-264 (FEP-100 Task Force II, Blend 90.78% purity	420045-03	No evidence of induction of unscheduled DNA synthesis. Dose levels tested 5, 10, 25, and 50 ug/mL in rat primary hepatocytes.		Acceptable 009789

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
85-1 Metabolism Species: rat Biol. Testing Cen.; Irvine, Ca P01930 & P01933; 04/30/90	14C-MGK 264 [14C-label at Hexyl-1-14C or Norbornene -2,3-14C]	427297-01 427297-02 427297-03 427297-04 427297-05 427297-06	Rats were given single or repeated oral doses of either [Hexyl-1-14C] MGK 264 or [Norbornene-2,3-14C] MGK 264. In the single low and repeated low-dose groups, the majority of the radioactivity found in the urine was excreted within 36 hrs postdosing [Hexyl-1-14C] MGK 264 (40-60%) and [Norbornene-2,3-14C] MGK 264 (34-64%). In the single high-dose group, the majority of the radioactivity found in the urine was excreted within 48 hrs postdosing ([Hexyl-1-14C] MGK 264 (56-66%) and [Norbornene-2,3-14C] MGK 264 (57-68%)). In all dose groups, the majority of the radioactivity found in the feces was excreted between 12 and 48 hrs postdosing ([Hexyl-1-14C] MGk 24 (17-44%) and [Norbornene-2,3-14C] MGK 264 (22-48%)). There were sex related differences in the elimination of MKG 264 in the urine and feces. By 168 hrs postdosing, females excreted more of the recovered radioactivity in the urine, whereas males excreted more of the radioactivity in the feces. At 7 days postdosing, total recovery of radioactivity was 93-97% for [Hexyl-1-14C] MGK 264 and 94-100% for [Norbornene-2,3-14C] MGK 264. Less than 0.5% of 14C remained in the tissues for both [Hexyl-1-14C] MGK 264 and [Norbornene-2,3-14C] MGK 264. The highest tissue levels of MGK 264 were found in the intestines and liver. Four major metabolites were identified in the urine and feces. Metabolite A contains a carboxylic acid formed by beta-oxidation of the side chain & an epoxide formed by oxidation of the norbornene ring double bond. Metabolite B is an isomer of Metabolite A. Metabolite C is formed by omega-1 oxid. of the side chain to produce a carboxylic acid & oxidation of the norbornene ring double bond to produce an epoxide. Metabolite D is an isomer of Metabolite C.		Minimum 010583
85-2 Metabolism - dermal absorption Species: rat Biol. Testing Cen.; Irvine, Ca P02072; 05/06/92	C14 radiolabeled [Hexyl-1 -C14]MGK 264 (Code; F.Q. 6188; 99% pure; cold MGK lot 3843, 93.1% pure	423465-01	Dermal admin. of [hexyl-1-14C] MGK 264 in CD rats resulted in slow absorption and excretion through enterohepatic circulation in the urine and feces. The calculated half-life was 31 hrs. The mean % dose absorbed at the 12, 43, 74 and 168 hrs following dosing, was 12.02, 34.36, 50.91 and 84.14% respectively; the % of dose excreted in both the urine & feces was 4.89, 28.41, 42.91 and 82.18%, respectively. The liver and intestines were identified as main organs of metabolism and excretion. There was no radioactivity buildup in other tissues.		Acceptable 009646

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
85-2 Metabolism - dermal absorption Species: rat Biol. Testing Cen.; Irvine, Ca P02073; 07/27/92	14C[Hexyl-1-14C]-MGK 264	424938-01	Absorption, distribution, excretion, and the balance of radioactivity at various time intervals were studied in rats given multiple dermal doses of 12 or 17 mg/kg of nonradiolabeled MGK 264, respectively, for 14 consec utive days followed by a single dermal dose of 12 or 17 mg/kg [Hexyl-1-14C] MGK 264, respectively, on day 15. Dermally applied MGK 264 was slowly & continuously absorbed through the skin & excreted mainly in the urine (51.48-69.29% od the dose), with lesser amounts excreted in the feces (27.65-30.37% of the dose). Total recovery of radioactivity was high (99.40-104.96% of the dose) at each time interval. During the 1st 12 hrs, 16% of the dose was absorbed followed by 0.4-0.5% absorption/hr for the duration of exposure (measured for 168 hrs). During 168 hrs, 84-98% of the dose was absorbed. Excretion of MGK 264 was rapid. MGK 264 does not accumulate in the tissues of rats as shown by the decrease in tissue radioactivity with time. By 168 hrs postdosing, <= 2.2% was recovered in the tissues. MGK 264 also does not accumulate in treated skin. A comparison of the results of this multiple-dermal-dose study with those of a single-dermal-dose study (13.6 mg/kg) (BTC Study P02072) showed that the patterns of absorption, tissue distribution, & elimination were comparable. For both dosing regimens, the dermal penetration of MGK 264 was time dependent -- the percent recovery of radioactivity in urine & feces incr. with time, whereas the recovery from the treated skin & skin washings decreased with time. The only major difference was that the amounts of radiaoctivity present at each time interval in the treated skin of animals were greater in the multiple-dermal-dose study than in the single dermal-dose study.		Acceptable 010393
85-2 Metabolism - dermal absorption Species: humans Pharma Bio. & Res. Testing Cen PBR-910205-3; 06/18/92	14C-labeled MGK-264 formulated with DEET and MGK-326	429767-02	Four male volunteers were admin. topical applications on the forearm of MGK-264 (14C (hexyl labeled), 0.069 mg/kg) formulated with DEET and MGK-326 and the material was kept on the skin for 8 hrs. An apparently thorough analysis of the blood, skin, washings, urine and feces indicated that 83.84 to 94.38% of the admin. dose was recovered. Only 0.29 to 0.051% of the dose was recovered in the urine and none was recovered in the feces. Based on the 6-16% unrecovered material which is assumed to be retained in the body and the amount in the urine, a dermal absorption factor for MGK-264 formulated with DEET and MGK-326 of 10% is assigned. Urinary metabolites were identified as isomeric products of beta oxidation and epoxidation of the norborene double bond.		Acceptable 010886

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
85-2 Metabolism - dermal absorption Species: human Pharma Bio. & Res. Testing Cen PBR-910204-2; 06/18/92	14C-labeled MGK-264	429767-01	Four human volunteeers were admin. topical applications on the forearm of MGK-264 (14C hexyl labeled, 0.067 mg/kg) and the material was kept on the skin for 8 hrs. An apparently thorough analysis of the blood, skin, washings, urine and feces indicated that 91.11 to 93.03% of the admin. dose was recovered. Only 1.11 to 2.32% was recovered in the urine and none was recovered in the feces. Based on the 7-9% unrecovered material which is asumed to be retained in the body and the amount in the urine, a dermal absorption factor for MGK-264 of 10% is assigned. Approximately 65% of the urinary metabolites were as being the same as rat urinary metabolites representing isomeric products of beta oxidation and epoxidation of the norborene double bond. Only about 1% of the urinary metabolites were unmetabolized MGK-264 with the remaining (about 35%) uncharacterized.		Acceptable 010886
86-1 Dom. animal safety env. exp. Species: dogs & cats Fementa Res. Cen.; #2229 9/7/90	Fenoxycarb 1%; Permethrin .15%;Pip. butox .50%; Caswell 613 1.0%; Caswell 025A 0.1%; Casw 400, 0.2%	416374-01	Groups of cats & dogs (each consisting of 1 adult male, 1 adult female, 3 mlae & 3 female kitens/puppies) were sprayed with the proposed formulation or a 4X conc: of its active ingredients or the vehicle (nonactive) components on days 0, 7 & 14 of a 21 day study. For dogs, individual applications (of either the vehicle, 1X or 4X formulations) ranged from 11.12 to 25.76 grams; for cats the corresponding values were 3.25 to 17.6 gms. In terms of the active ingred. Fenoxycarb single doses ranged from 0.0018 to 0.0100 g/kg at 1X, and from 0.0067 to 0.0415 g/kg at 4X. Possible symptoms observed only in a few dogs exposed to 1X & 4X formulations (and only in periods immediately after spraying): slight serous ocular discharge, panting, slight erythema on the lower abdomen. For cats only depression (highest level recorded defined as 'moderately depressed, lies down mostly, will stand') appeared to be correlated with exposure to the actives (observed only in a few kittens of the 1X & 4X groups on days 0-2, 7 & 14). Occurrence of matted hair in 4X cats & kittens, along with observation of 'oily' hair, particularly for a few days after spraying on day 14, suggests grooming behavior differences. While no significant adverse effects in cats and/or dogs were observed as a result of normal use-application of the proposed product, a point of toxicological concern is with 'inerts' in this formulation. Application of the 4X concentrate resulted in an exposure to 'inerts' equivalent to only that occurring with a 1X exposure. No information provided as to rate of delivery of this product (from a pum-sprayer). Comment in report (p. 13) as to 'the inherent inaccuracy of spray application' is also a point of concern. Not acceptable without additional information.		Unacceptable 008238

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
86-1 Dom. animal safety env. exp. Species: cat (kittens) 3/6/91 2239	Cas 652C .1%; 025A 0.1%; 652BB .15%; 670 0.5%; Cas 400 .2%; N-octyl bicyclo-heptene dicarboximide 1%		Six kittens (14-17 weeks old, weighing between 2.6 & 3.8 lbs) were sprayed 4 times with the formulation, with sufficient time between spraying for he formulation to dry. Total time elapsed between 1st and 4th spray for any one kitten was no more than 2 hrs & 15 min. Individual single applications ranged from 3.02 to 6.52 gms; cumulative applications ranged from 13.02 to 24.59 gms. One kitten (subsequently diagnosed to have a respiratory tract infection) was slightly depressed following the 4th spraying. The minimum rectal temperatures observed in 5/6 kittens (exception was the kitten with the infection) were observed on the day following spraying, but were still within normal range. A 'chalky' hair coat appearance was observed in 4/6 kittens following the 4th spraying, but was no longer detectable the second day after treatment. No significant toxicological effects were observed in any of the kittens; this study, with the previously reviewed studies, demonstrates that there is a reasonably adequate margin of safety (4X) associated with the normal use of this product in kittens. Acceptable when combined with previously reviewed material.		Acceptable 008304
86-1 Dom. animal safety env. exp. Species: dog Kansas State Univ. 11/14/89	Pyrethrins 0.14%; Tetra-methrin 0.063%; Pip but. 1%; Fenoxycarb 0.15%; N-octyl bicylohep.. 1.00%	422439-01	Groups of 4M, 4F dogs received a single 1X, 3X, or 10X normal-use application of the product. There was a control group consisting of 3M and 3F which were sprayed with a placebo formulation. Following spraying, animals were observed for 14 days. There were no symptoms of toxicity, even in the 10X group, & there were no indications of any effects on such parameters as body weight, food consumption, hematology, clinical chemistry or urinalysis.		Acceptable 010222

PENDING REGISTRATION INFORMATION IS NOT INCLUDED

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CASWELL#: 613
CAS-REG#: 113-48-4

P.C. CODE 057001- N-Octyl bicycloheptenedicarboximide FILE LAST PRINTED: 11/14/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
[redacted]					

PENDING REGISTRATION INFORMATION IS NOT INCLUDED