03/08/90

007739

PEER REVIEW FILES

CHEMICAL NAME: Guthion (Azinphos-methyl)
CASWELL NO.: 374
CAS NO.: 86-50-0
REVIEWER: Landolt/Ritter

CURRENT AGENCY DECISION

D; repeat of the rat study is requested (HED).

TUMOR TYPE / SPECIES

Follicular cell thyroid gland tumors; Islet cell adenomas or carcinomas of the pancreas; Osborne Mendel rats (M).

REVIEWER PEER REVIEW PACKAGE	PEER REVIEW MEETING DATE	PEER REVIEW DOCUMENTS	PEER REVIEW CLASSIFICATION
5. / /	5. / /	5. / /	5.
4. / /	4. / /	4. / /	4.
3. / /	3. / /	3. / /	3.
2. / /	2. / /	2. / /	2.
1. 05/23/86	1. 05/28/86	1. 06/19/86	1. D

SAP MEETING	SAP CLASSIFICATION
2. / /	2.
1. / /	1.

QUALITATIVE/QUANTITATIVE RISK ASSESSMENT DOCUMENT	GENETIC TOXICITY ASSESSMENT DOCUMENT
2. / /	1. / /
1. / /	

MISCELLANEOUS:

Stamped 2/6/90; #PR-007739; 105 p.; mha.

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4

Peer Review Documents
(Memo dates)

6/19/86

037739

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

JUN 19 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Abbreviated Peer Review Meeting on Guthion

John A. Quest, Team Leader
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769C)

TO: Larry Schnaubelt, Product Manager
Insecticide/Rodencide Branch
Registration Division (TS-767C)

The Toxicology Branch Peer Review Committee met on May 28, 1986 to review the toxicology data base on Guthion (Azinphosmethyl).

1. Committee members in attendance were:

Their signature indicates concurrence with the preliminary finding and conclusions concerning Guthion.

Anne Barton

William Burnam

Reto Engler

Theodore Farber

Bernice Fisher

Bertram Litt

John Quest

Esther Rinde

Dave Ritter (Reviewer)

Bruce Jaeger (Section Head)

2. Background:

Guthion is an organophosphate insecticide that has established tolerances for a substantial number of crops and for meat, milk, and meat by-products. The data base for Guthion is insufficient for the purpose of performing a full

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weight-of-the-evidence (WOE) evaluation, but the available information has previously raised some concern about the oncogenicity of the chemical. The Peer Review Committee performed a preliminary evaluation of the limited information that was available, reached a preliminary consensus opinion regarding an oncogenicity classification for Guthion according to EPA proposed guidelines (CFR, November 23, 1984), and identified toxicology data gaps that need to be filled in order to perform a definitive WOE evaluation in the future.

3. Oncogenicity Studies

Three oncogenicity studies were performed on Guthion. These included (1) a rat study and (2) a mouse study, both of which were performed by Gulf South Research Institute GSRI as part of the NCI Bioassay Program; and (3) a second mouse study performed by Mobay Chemical Corporation.

In the GSRI rat study, groups of 50 male and 50 female Osborne Mendel rats received dietary doses of 78 or 156 ppm (males) and 62.5 or 125 ppm (females) for 80 weeks, and were then observed for an additional 34-35 weeks. Concurrent control groups consisted of 10 rats/sex. Additional "pooled" controls of 95 rats/sex were also included. Guthion produced: (a) significantly elevated incidences of follicular cell thyroid gland tumors in low and high dose male rats when compared with pooled controls (pooled controls, 7/86 or 8.1%; matched controls, 1/9 or 11.1%; low dose, 10/44 or 22.7%; high dose, 12/43 or 27.9%); and (b) a significantly elevated incidence of islet cell adenomas or carcinomas of the pancreas in the high dose male rats when compared with pooled controls (pooled controls, 2/88 or 2.2%; matched controls, 0/9 or 0%; low dose, 1/47 or 2.1%; high dose 6/44 or 13.6%). However, since the spontaneous incidences of these lesions varied in Osborne-Mendel male rats at GSRI (i.e. range of 0% to 43% for thyroid tumors and range of 0% to 22% for islet cell tumors), the NCI report on Guthion (Azinphosmethyl) concluded that the "neoplasms of the thyroid and pancreatic islets suggest but do not provide sufficient evidence for the carcinogenicity of Azinphosmethyl in male Osborne-Mendel rats." The Committee made the following additional observations regarding the study: (1) the use of pooled control animals was probably inadequate for comparative purposes because of variations in the experimental conditions under which animals were studied before they were selected for inclusion in the pooled control group; (2) an insufficient number of concurrent (i.e., matched) control animals were tested in this study; and (3) a corn oil vehicle was used in this feeding study, and this vehicle is known to produce pancreatic islet cell tumors in rats.

In the GSRI mouse study, groups of 50 male and 50 female B6C3F$_1$ mice received dietary doses of 31.3 or 62.5 ppm (males) and 62.5 or 125 ppm (females) for 80 weeks, and were then observed for an additional 13 weeks. Concurrent control groups consisted of 10 rats/sex. Additional "pooled" controls of 120-130/sex were also included. Guthion was negative for oncogenicity in this study.

In the Mobay mouse study, group of 50 male and 50 female CD-1 mice received dietary doses of 0, 5, 20 or 40 ppm (80 ppm for the first week) for 2 years. A preliminary review indicated that Guthion was negative for oncogenicity in this study.

4. Ancilliary Data for WOE Determination:

The mutagenicity of Guthion was evaluated only in an unscheduled DNA synthesis test using primary rat hepatocytes, and negative results were obtained. No metabolism data allowing for SAR determinations were available.

5. Additional Toxicity Data:

Other information in addition to oncogenicity data was also discussed. A 105 week toxicity study in male and female Cocker Spaniel dogs (0, 5, 39.7 and 135.7 ppm; doses are time-weighted average doses) resulted in findings of RBC ChE inhibition (mid and high doses), muscle tremors plus head drop and staggering (high dose), and reduced food consumption and body weight after 85 weeks (high dose). The NOEL was 5 ppm. A mouse three-generation reproduction study was also performed (dietary doses 0f 0, 5. 10 or 25 ppm) and no adverse effects were observed. No other toxicological information was available for review by the Committee.

6. Conclusion:

On the basis of the limited data base available for Guthion, the Peer Review Committee concluded that the chemical be classified tentatively as a Category D carcinogen (inadequate animal evidence of carcinogenicity). The category D classification was assigned on a interim basis because only suggestive (but not definitive) evidence of oncogenicity was seen in a rat chronic bioassay where questionable and/or inadequate control groups were used, and because two additional mouse chronic bioassay were negative for an oncogenic effect. In addtion, insufficient additional supporting toxicological data was available to assist in the determination on oncogenic potential.

7. Additional Data Required for a Definitive WOE Determination:

The Committee recommended that additional data must be submitted by the registrant to permit a full weight-of-the-evidence (WOE) evaluation of Guthion and a final oncogenicity classification according to EPA proposed guidelines.

The primary data needed to further define the oncogenic potential of Guthion is a repeat 2 year oncogenicity study in rats. This rat oncogenicity study should be performed according to Subpart F guidelines in a strain of animals for which there is an adequate historical control data base. A vehicle other than corn oil should be employed.

Ancilliary data needed for inclusion in the WOE determination are additional mutagenicity studies which include gene mutation tests and chromosome abberation tests, and metabolism studies. Teratology tests in two species, and neurotoxicity studies, are also required to complete the data base on Guthion.

#11 6/2/86 sb

Reviewer's Peer Review Package for 1st Meeting

5/23/86

~~Dinoseb~~

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

007739

MAY 23 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Abbreviated Peer-Review of Guthion and Dinoseb

FROM: Reto Engler, Chief
Mission Support Staff
Toxicology Branch, HED (TS-769)

TO: Addressees

The data base for both Guthion and Dinoseb is insufficient to perform a conclusive weight-of-the-evidence. However, the information at hand indicates, or has indicated in the past some concern on the chemical's oncogenicity.

Therefore an abbreviated peer-review is indicated based on the present knowledge. This review should provide a preliminary consensus evaluation and a listing of additional information which is deemed necessary to perform a definitive weight-of-the-evidence evaluation.

Attached for your review are two packages on the above chemicals. The Review Group is scheduled to meet in Dr. Farber's office on May 28, 1986 at 2:00 p.m.

Attachments

Addressees:

Theodore Farber
William Burnam
Jack Quest
B. Litt/Fisher
Anne Barton
Jim Rowe
Winnie Teeters
David Ritter

AZINPHOS METHYL MINI-PEER REVIEW

AZINPHOSMETHYL (Guthion), the generic name for O,O-dimethyl-S-[(4-oxo-1,2,3-benzotriazin-3-(4H)-yl)methyl]phosphorodithioate, is a widely used organophosphate insecticide with established tolerances of up to 10.3 ppm in a substantial number of crops and in meat, milk and meat byproducts. The chemical is an intense cholinesterase inhibitor in mammals and is a Category I toxicant by the oral and dermal routes of exposure with LD_{50}s of 4.6 mg/kg and 4.4 mg/kg for males and females, respectively, for acute oral toxicity and 200/250 mg/kg and 155 mg/kg for males and females, respectively, for acute dermal toxicity.

CHRONIC/ONCOGENICITY STUDIES

Osborne-Mendel rats and B6C3F1 mice Azinphos-methyl was assayed for oncogenicity at the Gulf South Research Institute (GSRI) under contract to the NCI.

Rats

Groups of 50 male and 50 female rats were offered diets containing Guthion at 78 or 156 ppm (time weighted average) for males and 62.5 or 125 ppm for females. Concurrent control groups consisted of ten rats per sex. The animals were fed for 80 weeks, and then observed for an additional 34 or 35 weeks. Additional "pooled" controls of 95 animals per sex were included. Signs of organophosphate exposure included hyperactivity, tremors and dyspnea. Doses for the male rats rats were reduced at 20 weeks because of Guthion-related effects.

Tumors were reported for the adrenal glands, follicular cells of the thyroid in dosed males and females and in the anterior pituitary and the parathyroids of dosed males; the latter was statistically significant when compared to the incidence of this lesion in the pooled controls but not when compared to that of the concurrent controls. These effects were not considered to be compound-related.

Adenomas and adeno-carcinomas were reported for the pancreatic islet cells in numbers that suggested, but did not clearly establish, that Guthion is an oncogen in male rats. Time-adjusted analyses (eliminating rats dying before week 52) were calculated for adenomas and adenocarcinomas as follows:

Pooled Controls	2/88 (males)	2 %
Concurrent Controls	0/9 "	0 %
Low dose	1/47 "	2 %
High dose	6/44 "	14 %

NCI reported that the Cochran-Armitage trent test was positive using either the pooled ($p = 0.008$) or the matched ($p = 0.015$) controls. Fischer's Exact test was significant ($p = 0.015$) between matched controls and the high dose male rats.

NCI then tends to discount these findings by stating that since the historical control data for male Osborne-Mendel rats at GSRI for these lesions ranges from 0 % to 22 % with a mean of 2 % , it is doubtful that the increase in pancreatic tumors is Guthion-related.

Increases in other tumor in male rats were noted as follows:

Adrenal carcinoma or cortical adenoma:

Pooled Controls	3/95 (males)
Concurrent Controls	1/9 "
Low dose	4/45 "
High dose	10/46 "

Thyroid - all follicular cell tumors:

Pooled Controls	3/95 (males)
Concurrent Controls	1/9 "
Low dose	4/45 "
High dose	10/46 "

The attached discussion by NCI presents their opinion about these tumors and concludes by stating that "... statistical tests suggest that the increase of thyroid and pancreatic islet-cell tumors in male rats are associated with administration of Azinphos-methyl".

Subsequently, NCI states that these increases, when evaluated in terms of historical controls tend to "... suggest but do not provide sufficient evidence for carcinogenicity of Azinphos-methyl in male Osborne-Mendel rats.

Mice

1. Groups of 50 male mice were offered diets containing 31.3 or 62.5 ppm Guthion in the diet for eighty weeks, followed by a recuperation period of 13 weeks. A similar group of 50 female mice were offered diets containing 62.5 or 125 ppm under a similar regimen. A concurrent control group consisted of ten mice of each sex. A "pooled" control group consisted of 130 males and 120 females. There was no increased incidence of tumors that could be attributed to exposure to Guthion.

2. A recent oncogenicity assay in CD1 mice was performed by Mobay (1985). Guthion was fed to mice at 0, 5, 20 or 40 ppm (80 ppm for first week) for two years. A preliminary review indicates that there was no statistically significant increase in tumor incidence that could be attributed to Guthion ingestion. Significant ChE inhibition was seen at 20 and 40 ppm for plasma, red cell and brain; thus there was a clearly demonstrated maximum tolerated dose. Survival rates were similar for all groups; there was no Guthion-related effects on any parameter except that on ChE inhibition.

Chronic Dog Feeding Study

Four groups of 4 pedigree Cocker Spaniel dogs per sex were offered diets containing Guthion as follows: 0 ppm (control) and 5 ppm (low dose) for 105 weeks (TWA = 5 ppm); 20 ppm for 36 weeks then 50 ppm for 69 weeks (mid-dose; TWA = 39.7 ppm); and 50 ppm for 36 weeks, 100 ppm for 21 weeks, 150 ppm for 27 weeks and 300 ppm for the final 21 weeks (high-dose; TWA = 135.7 ppm). Animals were subjected to standard toxicological evaluation under satisfactory GLP conditions. compound ingestion. Clinical signs included fine muscle tremors of the hind limbs, drooping of the head and staggering. These signs appeared in the high-dose animals only. Body weight and food consumption were similar for the control and low and middle dose animals but these measurements were reduced in the high-dose animals after the dosage was increased to 300 ppm at week 85. RBC ChE inhibition was noted in the mid- and high-dose animals. No other adverse effects were reported for any clinical or histopathological parameters (MRID 00083620). No tumors were reported in any animal. The No Observed Effect Level in this study is 5 ppm (TWA).

NEUROTOXICITY

There are no valid neurotoxicity studies available for Guthion, neither are there valid antidote studies.

REPRODUCTION/TERATOLOGY

A mouse multi-generation reproduction study revealed that animals offered diets containing 0, 5, 10 or 25 ppm Guthion showed no adverse effects over three generations on reproductive indices (50 ppm proved to be too toxic to continue, inducing 62.5% mortality). This study was found to be deficient in reported data and was classified as supplemental.

MUTAGENICITY

Unscheduled DNA Synthesis

Guthion did not produce a significant degree of nuclear labeling in primary rat hepatocytes when tested at levels of 0.25 to 50.3 ug/ml. 2-AAF, the positive control induced unscheduled DNA synthesis at a level of 0.05 ug/ml. This study partially satisfies the requirement of 84-2. Gene mutation studies and Chromosomal aberration studies remain outstanding.

GENERAL METABOLISM

There are no valid metabolism studies; therefore a data gap exists for this requirement (85-1).

WEIGHT OF EVIDENCE REVIEW

1) Based on the fact that the rat study cited above provides suggestive but not definitive evidence of oncogenicity and 2) both the NCI mouse and the new Mobay mouse study were negative for oncogenic effect, a complete Peer Review and Weight-of-Evidence review of Guthion is not at present possible. We therefore recommend that the pesticide be placed tentatively in category "D" until all necessary data, such as another onco/chronic rat study, additional mutagenicity assays and metabolism studies are submitted and evaluated.

I asked Litt to do Incr. assessment, 0077

374

MEMORANDUM

DATE: 10/28/80

SUBJECT: Guthion for Use on Carrots
Section 18 Request and IR-4 Petition

FROM: Bertram D. Litt, Statistician
Toxicology Branch/HED (TS-769)

TO: Douglas D. Campt, Director
Registration Division (TS-767)

THRU: William L. Burnam, Acting Chief
Toxicology Branch/HED (TS-769)

Peter E. McGrath, Director
Hazard Evaluation Division (TS-769)

An incremental risk assessment is summarized below for guthion on carrots relating to the Section 18 request from Maryland and the IR-4 Tolerance Petition (6E1765). A more detailed, documented, report of this risk assessment will be available shortly. The subject risk assessment is based on the two year incidence of benign and/or malignant pancreatic islets cell tumors in the male Osborne-Mendel rats reported in NCI "Bioassay of Azinphos methyl for Possible Carcinogenicity, NCI-CGR-TR-69". Although the study may be criticized because of the small size of the matched control groups (10 per sex per species) and the change of dosage after the first 20 dosage weeks, the finding of excess (P=.015 comparison of high dose to pooled controls) numbers of pancreatic islets cell tumors and a dose-related response (P=.008 relative to pooled controls and P=.033 relative to the matched controls) is present. This finding cannot be discounted by toxicity reported earlier during the study.

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To estimate risks to the U.S. population groups who may consume carrots treated with guthion, the assumptions and procedures recommended by the Cancer Assessment Group have been followed in performing low-dose extrapolation of the animal data and further extrapolation to humans. Extrapolation to low-dose risks of tumors in the experimental rat strain by several procedures demonstrates that the estimates of Virtually Safe Dose levels of guthion may vary by as much as 7 orders of magnitude depending upon the mathematical model. The expression "Virtually Safe Dose" was used by Mantel and Bryan in JNCI Vol. 27, No. 2, August 1961 as the qualitative judgement of the level of risk that society would be willing to tolerate. Their example was the 1/100,000,000 level of risk at the statistical assurance level of 99%. They showed methods for computing maximum p value 99% assurance levels, or the upper 99% confidence bound, for the risk associated with dose levels ranging from 10^{-3} to 10^{-8}. In this risk assessment the same relationship is expressed by the lowest dose, estimated by the lower 99% confidence bound, associated with the specific risks of tumors. For example, when the expected number of tumors, or risk to people, is 1×10^{-4}, the following estimates of the Virtually Safe Dose of guthion are found:

Mantel-Bryan Procedure	1.5×10^{-1} ppm
Multi-Stage Model	4.9×10^{-2} ppm
One-Hit Model	2.4×10^{-6} ppm

When the expected risk is 1×10^{-8}, the estimates of Virtually Safe Dose levels for guthion are:

Mantel-Bryan Procedure	1.9×10^{-3} ppm
Multi-Stage Model	4.9×10^{-6} ppm
One-Hit Model	2.4×10^{-10} ppm

Of the two parametric models (one-hit and multi-stage) the multi-stage model provides a better fit to the observed study data. Furthermore, there is no reason to assume that the non-parametric Mantel-Bryan procedure provides better estimates in the unobserved low-dose range than do parametric models. For these reasons, the multi-stage model is used for our extrapolation of cancer risks associated with the use of guthion on carrots.

A. To estimate the risk of cancer in rats at low-doses of guthion the average daily exposure of 104 ppm guthion was calculated from the lifetime adjusted daily dose:

(20 wks. x 250 ppm) + (80 wks. x 125 ppm) ÷ 120 wks. = 104 ppm

B. Food factors and tolerance levels were used to estimate cancer risk in humans. As the NCI reports the Azinphos methyl (Guthion) study dosage in terms of the ppm mixed into the diet without specification of the units consumed, no further interspecies correction factors were considered appropriate (see Mantel and Schneiderman footnote to page 1380; Cancer Research; Vol. 35; 1975). To estimate the maximum average daily exposure of guthion from carrots, we multiply the food factor of 0.43 percent for carrots (see Revised Tables in R.D. Schmitt memo, 1977) by the proposed tolerance level of 0.5 mg per kg (or ppm), i.e. .0048 x 0.5 mg/kg = .0024 ppm guthion per day.

Secondly, we consider the implication of starting to eat guthion treated carrots during the first year of life: the average daily exposure to guthion in carrots computed for the first two years of life is 14.7 times that computed above.

C. The USDA spring 1977 estimate of carrot intake (i.e. Deep Yellow Vegetable intake used as the estimate for carrots) for children aged 0-1 and 1-2 years was multiplied by the proposed tolerance. The product was then adjusted by dividing it by the kg of total food consumed as calculated by the USDA for these age categories (USDA Food Consumption Survey Spring 1977). The two estimates were then averaged:

.076 kg carrots x 0.5 mg Guthion/kg carrots		= 0.038 mg
Guthion age 0-1:	0.038 ÷ .989 kg food	= .0387755
age 1-2:	0.038 ÷ 1.195 kg food	= .03179915
age 0-2:		= .035283 mg Guthion per kg food consumed

Thirdly, we consider that if it was unrealistic to estimate risks for people based on the average lifetime adjusted doses without adjustment for the age cohort at which the risk began, it might also be an error to time-adjust the exposure to study animals.

D. It may be that in an experiment such as this, where a high dosage is administered for 20 weeks, sufficient exposure may have been administered to induce the tumors which are observed later in the study. If that were true then the use of the higher initial dosage level as the basis for the risk assessment would be more realistic and would lead to lower estimates of risk to the study animals and to humans.

The following Table depicts the human risks estimated under the assumptions discussed in paragraphs A, B, C and D above. The human THRC estimates described in paragraphs B and C are cross-referenced to the animal exposure estimates in paragraphs A and D.

Human Guthion Exposure		Upper 99% Guthion Limit on Extrapolated Tumor Risk From Rat Exposures of:	
Source	Guthion Exposure mg/kg/day	0/52/104 ppm (A)	0/125/250 ppm (D)
11/5/79 Printout of all Foods, THRC	0.4557 (B)	9.266×10^{-4}	3.850×10^{-4}
THRC for Carrots Alone	0.0024 (B)	4.869×10^{-6}	2.026×10^{-6}
Total THRC Carrots	0.4521 (B)	9.315×10^{-4}	3.870×10^{-4}
Yr.1,2 Carrot Intake	0.0353 (C)	7.163×10^{-5}	2.980×10^{-5}
Total + yr.1,2,	0.4910 (C)	9.986×10^{-4}	4.148×10^{-4}

(THRC = Theoretical Maximal Residue in Contribution PPM)

Summary

Carrots (Section 18 and IR-4 Tolerance Petition 6E1768)

The tumor risk from carrots treated with guthion may be as low as 2.03×10^{-6} or it may be as high as 7.16×10^{-5}. The quality of the data in this experiment suggests that the intermediate value of 2.98 or 3×10^{-5} be used as our most defensible estimate of the incremental risk. Thus, if 1×10^{-6} is taken as the Agency standard for an acceptable level of risk the guthion exposures from treated carrots would be unacceptable for the entire population that might eat treated carrots. However, if 1×10^{-5} is taken as the Agency standard, the acceptable level of risk would be exceeded for young children but not for adults.

All Foods

The lowest overall estimate of risk, 3.9×10^{-4}, for all foods suggests that if the analytically determined guthion residues in the prepared foods approximate the TMRC estimates of exposure; the risk of carcinogenesis may suggest a need for reduction of some uses.

cc: Ann Barton

TS-769:LITT:slv:CH#2:RH.816:X73710:10/24/80

SUMMARY

A bioassay of technical-grade azinphosmethyl for possible carcinogenicity was conducted by administering the test chemical in feed to Osborne-Mendel rats and B6C3Fi mice.

Groups of 50 rats of each sex were administered azinphosmethyl at one of two doses for 80 weeks, then observed for 34 or 35 weeks. Time-weighted average doses of either 78 or 156 ppm were used for the males. Initial doses of 62.5 or 125 ppm used for the females were maintained throughout the bioassay. Matched controls consisted of groups of 10 untreated rats of each sex; pooled controls consisted of the matched controls combined with 95 male and 95 female untreated rats from similar bioassays of 10 other test chemicals. All surviving rats were killed at 114 or 115 weeks.

Groups of 50 mice of each sex were administered azinphosmethyl at one of two doses for 80 weeks, then observed for 12 or 13 weeks. The doses were either 31.3 or 62.5 ppm for the males and either 62.5 or 125 ppm for the females. Matched controls consisted of groups of 10 untreated mice of each sex; pooled controls consisted of the matched controls combined with 130 male and 120 female untreated mice from similar bioassays of 11 other test chemicals. All surviving mice were killed at 92 or 93 weeks.

High- and low-dose male rats and mice and high-dose female rats and mice had lower mean body weights than corresponding matched controls throughout the bioassay. Typical signs of organophosphate intoxication were observed in a few animals of both species, and included hyperactivity, tremors, and dyspnea. Sufficient numbers of animals were at risk in each species for development of late-appearing tumors.

A great many tumors of the endocrine organs were observed in both dosed male and dosed female rats. Those of the adrenal in dosed males and females, the follicular cells of the thyroid in dosed

females, the anterior pituitary in dosed males, and the parathyroid in dosed males occurred at statistically significant incidences when compared with pooled controls, but not with matched controls, and they were not considered to be related to administration of the test compound. The incidences of tumors of the pancreatic islets and of the follicular cells of the thyroid in the male rats suggest, but do not clearly implicate, azinphosmethyl as a carcinogen in these animals.

In mice of each sex there were no increased incidences of tumors that could be related to administration of the test chemical.

It is concluded that under the conditions of this bioassay, neoplasms of the thyroid and pancreatic islets suggest but do not provide sufficient evidence for the carcinogenicity of azinphosmethyl in male Osborne-Mendel rats. Azinphosmethyl was not shown to be carcinogenic in female Osborne-Mendel rats or in B6C3F1 mice of either sex.

does not appear to be related to the administration of azinphosmethyl.

A variety of nonneoplastic responses were represented among both matched-control and dosed animals. Such lesions have been encountered previously and are considered to be spontaneous events, not unlike those commonly observed in aging Osborne-Mendel rats.

Based on the histologic examination, there was no evidence for the carcinogenicity of azinphosmethyl in Osborne-Mendel rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% in one or more than one group.

In some instances, the matched-control group had incidences of tumors significantly higher ($P < 0.05$) than those in the pooled-control group, exclusive of the matched controls. These instances are indicated in tables E1 and E2 by the symbol "g" placed beside the incidence shown for the matched controls. This test was conducted assuming a binomial distribution of spontan-

eous tumors with the parameter given by the pooled controls excluding the matched controls of the subject chemical (Fears et al., 1977). In other instances, the matched controls were not statistically different from the pooled controls, but had a higher incidence or an incidence comparable to one or more of the dosed groups. When the incidence in the matched controls either is significantly higher than that in the pooled controls or is comparable to that in the dosed groups, the significance generated by the use of the pooled controls has been discounted in the analysis.

In male rats, the result of the Cochran-Armitage test for positive dose-related trend on the combined incidence of islet-cell adenomas or carcinomas of the pancreas is significant, using either the pooled ($P = 0.008$) or matched ($P = 0.033$) controls. The result of the Fisher exact test comparing the incidence in the high-dose group with that in the pooled controls was also significant ($P = 0.015$). Time-adjusted tests, eliminating animals that died before week 52 on study, were performed on the incidences of tumors of the pancreatic islet. The time-adjusted incidences (pooled controls 2/88 [2%], matched controls 0/9, low-dose 1/47 [2%], high-dose 6/44 [14%]) resulted in essentially the same statistics as described for the non-adjusted tests.

Since, however, the spontaneous incidence of this lesion varies in male Osborne-Mendel rats at this laboratory from 0% to 22%, with a mean of 2%, the incidence found in the high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

The Cochran-Armitage analyses of the combined incidence of adenocarcinomas or cortical adenomas of the adrenal in male rats show significant results ($P < 0.001$) when the pooled-control group is used. The result is not significant using the matched-control group. The result of the Fisher exact comparison of the incidence in the high-dose group with that in the pooled controls indicates a probability level of 0.001; however, the results of the Fisher exact test are not significant when the incidence in the matched-control group is compared with that in each dosed group. In the incidence of adenocarcinoma of the adrenal alone, the result of the Cochran-Armitage test is significant ($P = 0.015$) using the pooled-control group, but not so when the matched-control group is used. The Fisher exact test comparing the incidence in the high-dose group with that in the pooled-control group indicates a P value of 0.033, which is above the 0.25 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. Therefore,

statistically, the association of the tumors in the adrenal is not well established. No such tumor is observed in female rats.

In male rats, the results of statistical tests using the pooled-control animals on the incidences of benign thyroid tumors (follicular-cell adenomas, adenomas, or cystadenomas), malignant thyroid tumors (adenocarcinomas, cystadenocarcinomas, or papillary cystadenocarcinomas), or the combined follicular-cell tumors are all significant. In each analysis, the result of the Cochran-Armitage test is significant ($P \leq 0.008$) using the pooled controls, and the results of the Fisher exact comparisons of the incidences in any of the dosed groups with the pooled-control group show probability levels less than 0.025. The results of the Fisher exact test comparing the incidence in the matched-control group with that in each dosed group are not significant. Time-adjusted analyses, eliminating animals that died before week 52 on study, were performed on the incidences of thyroid tumors. The analysis of time-adjusted data of 7/82 (9%) in the pooled-control group, 1/9 (11%) in the matched-control group, 14/44 (32%) in the low-dose group, and 14/43 (33%) in the high-dose group resulted in essentially the same statistics as those of the non-adjusted analysis. Since, however, the spontaneous incidence of these neoplasms varies in male Osborne-Mendel rats at this laboratory from 0% to 43%, with a

mean of 7%, the incidences found in low-dose or high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

In females, the results of the statistical tests on the combined incidence of the malignant thyroid tumors (adenocarcinomas, cystadenocarcinomas, or papillary cystadenocarcinomas) are not significant. The incidence in the matched controls does not differ statistically from that in the pooled controls. When the benign thyroid tumors are combined with the malignant tumors, the result of the Cochran-Armitage test on the combined incidence in female rats, using the pooled controls, is significant ($P = 0.008$), and the results of the Fisher exact test show that the incidences in the dosed groups are significantly higher (low-dose $P = 0.002$; high-dose $P = 0.021$) than that in the pooled controls. However, the incidence of 2/9 (22%) in the matched controls, higher than that of either dosed group, makes the significance seen in the use of the pooled controls questionable. Although the results of the statistical tests of the combined incidence of cystadenomas and adenomas in the thyroid are significant, the incidence seen in the matched controls is comparable to those in the dosed groups.

When the the number of female rats with some type of pituitary tumor (chromophobe adenomas, adenocarcinomas, adenomas, or

cystadenomas) are analyzed, the results of the Cochran-Armitage test are not significant, and the Fisher exact comparison of incidences in the low-dose and pooled-control groups indicates a probability level of 0.040, which is above the 0.025 level required by the Bonferroni inequality criterion when multiple comparison is considered. The incidence in the high-dose group is not significant.

In female rats, when hemangiomas and hemangiosarcomas are grouped for analysis, the results of the Cochran-Armitage test are not significant, but an indicated departure from linear trend is observed (P = 0.018), using the pooled controls, since the incidence in the low-dose group is greater than that in the high-dose group. The Fisher exact comparison of the incidences in the low-dose and pooled-control groups indicates a probability level of 0.036, which is above the 0.025 level required by the Bonferroni inequality criterion when multiple comparison is considered. The incidence in the high-dose group is not significant. The incidence of these tumors in the male rats is not significant.

Some incidences at specific tumor sites indicate a higher incidence in the matched controls than in the pooled controls (marked "g" in the tables) or a comparable or higher incidence in the matched controls than in the dosed groups. Under these

circumstances, the significance generated by the use of the pooled controls is questionable. The tumors which are not said to be dose associated, because of these reasons, are the pituitary tumors, the parathyroid tumors, and hemangiomas or hemangiosarcomas in male rats; along with the liver tumors, cortical adenomas in the adrenal, fibroadenomas of the mammary gland, tumors of the uterus, and tumors of the pancreatic islet in female rats.

In summary, the statistical tests suggest that the incidences of thyroid and pancreatic islet-cell tumors in male rats are associated with administration of azinphosmethyl. None of the tumors in females could be associated with the test chemical.

V. DISCUSSION

In this bioassay, azinphosmethyl had a toxic effect on both rats and mice, as demonstrated by depressed mean body weights, clinical signs, and/or lower survival. High- and low-dose male rats, high-dose female rats, and high-dose female mice had lower mean body weights than their corresponding controls throughout the study. Typical signs of organophosphorus intoxication were present in a few animals of both species and included hyperactivity, tremors, and dyspnea. Convulsions in the mice may have been related to organophosphorus intoxication, although they were also seen in one control male mouse. In male rats and in both male and female mice, tests for dose-related trends in mortality over the bioassay were not significant at the 0.05 level. In female rats, 50% of the high-dose animals survived until the end of the bioassay, compared with 68% of the low-dose animals and 70% of the controls. Sufficient numbers of animals were at risk in each species for development of late-appearing tumors.

A great many tumors of the endocrine organs were observed in both dosed male and female rats but the small size of the matched control groups made interpretation difficult. Those of the adrenal in dosed males and females, the follicular cells of the thyroid in dosed males and females, the anterior pituitary in dosed males, and the parathyroid in dosed males occurred at

statistically significant incidences when compared with pooled controls, but not with matched controls. Since the pathologist examining the dosed and matched-control animals did not examine the pooled controls, and since the incidences of the pituitary and parathyroid in males, and of the thyroid in females were significantly higher in the matched controls than in the pooled controls, these neoplasms cannot be clearly related to administration of azinphosmethyl. The incidence of adenocarcinoma of the pituitary in female rats cannot be clearly associated with administration of the test chemical, since the dose-related trend and the incidence of tumors in the high-dose group were not significant; also, the combined benign and malignant tumors of the pituitary occurred at a lower level of significance than the adenocarcinoma alone. Although the incidence of tumors of the liver showed a dose-related trend in the male rats, the incidences in the dosed groups were not significantly higher than those in the controls, and these tumors cannot, therefore, be clearly related to administration of the test chemical.

In male rats, islet-cell adenomas or carcinomas of the pancreas occurred at a significant incidence (P = 0.015) in the high-dose male rats when compared with pooled controls (pooled controls 2/92, matched controls 0/9, low-dose 1/47, high-dose 6/45), and

the incidences showed a dose-related trend (P = 0.008), using the pooled controls. Two of the high-dose males had carcinomas, while the remaining four had adenomas. Since, however, the spontaneous incidence of this lesion varies in male Osborne-Mendel rats at this laboratory from 0% to 22%, with a mean of 2%, the incidence found in the high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

Follicular-cell tumors of the thyroid, either benign (adenomas, follicular-cell adenomas, or cystadenomas), malignant (adenocarcinomas, cystadenocarcinomas, or papillary cystadenocarcinomas), or combined benign and malignant occurred at significant incidences in dosed male rats when compared with pooled controls; the combined tumors occurred at significant incidences (P = 0.001) in both low- and high-dose groups when compared with pooled controls (pooled controls 7/86, matched controls 1/9, low-dose 14/44, high-dose 14/43), and the incidences showed a dose-related trend (P < 0.001), using the pooled controls. Since, however, the spontaneous incidence of these neoplasms varies in male Osborne-Mendel rats at this laboratory from 0% to 43%, with a mean of 7%, the incidences found in low-dose or high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

In mice, hepatocellular adenomas or carcinomas occurred at a significant incidence (P = 0.040) in the high-dose male mice when compared with pooled controls (pooled controls 30/128, matched controls 2/3, low-dose 11/49, high-dose 19/50), and the incidences showed a dose-related trend (P = 0.048). Hepatocellular adenomas and carcinomas were diagnosed among the dosed and matched-control groups, and neoplastic nodules of the liver were diagnosed in addition in animals of the pooled-control group. The probability level of the liver tumors in the high-dose group is above that required for significance using the Bonferroni inequality criterion for multiple comparisons, and similar high incidences have been noted in other groups of controls at the same laboratory; thus, these liver tumors in male mice are not considered to be related to administration of the test chemical.

Azinphosmethyl is an organophosphorus chemical with a primary biological action of inhibiting acetylcholinesterase. This activity was very low when serum, homogenized brain, or submaxillary gland were tested in vitro; however, the chemical is rapidly oxidized in vivo to the active chemical (DuBois et al., 1957). In a 2-year feeding study using Wistar rats, there was no indication that administration of the chemical at concentrations up to 50-100 ppm induced tumors (Worden et al., 1973). This

concentration was comparable to that fed to the low-dose rats in the present study.

It is concluded that under the conditions of this bioassay, neoplasms of the thyroid and pancreatic islets suggest but do not provide sufficient evidence for carcinogenicity of azinphosmethyl in male Osborne-Mendel rats. Azinphosmethyl was not shown to be carcinogenic in female Osborne-Mendel rats or in B6C3F1 mice of either sex.

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma[b]	5/101 (5)	1/10 (10)	3/50 (6)	1/49 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.212	0.412
Lower Limit			0.194	0.009
Upper Limit			5.931	3.527
Relative Risk (Matched Control)[f]			0.600	0.204
Lower Limit			0.058	0.003
Upper Limit			30.890	15.723
Weeks to First Observed Tumor		115	68	113
Liver: Hepatocellular Adenoma[b]	3/99 (3)	1/9 (11)	3/49 (6)	5/46 (11)
P Values[c,d]	P = 0.044	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			2.020	3.587
Lower Limit			0.278	0.726
Upper Limit			14.484	22.059
Relative Risk (Matched Control)[f]			0.551	0.978
Lower Limit			0.055	0.139
Upper Limit			28.360	45.235
Weeks to First Observed Tumor		115	115	97

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	13/85 (15)	4/9 (44)[g]	21/46 (46)	13/43 (30)
P Values[c,d]	P = 0.012	N.S.	P < 0.001**	P = 0.042**
Departure from Linear Trend[e]	P = 0.004			
Relative Risk (Pooled Control)[f]			2.985	1.977
Lower Limit			1.581	0.920
Upper Limit			5.696	4.147
Relative Risk (Matched Control)[f]			1.027	0.680
Lower Limit			0.513	0.312
Upper Limit			3.432	2.420
Weeks to First Observed Tumor		103	102	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	13/85 (15)	4/9 (44)[g]	21/46 (46)	15/43 (35)
P Values[c,d]	P = 0.003	N.S.	P < 0.001**	P = 0.012**
Departure from Linear Trend[e]	P = 0.009			
Relative Risk (Pooled Control)[f]			2.985	2.281
Lower Limit			1.581	1.110
Upper Limit			5.696	4.634
Relative Risk (Matched Control)[f]			1.027	0.785
Lower Limit			0.513	0.371
Upper Limit			3.432	2.733
Weeks to First Observed Tumor		103	102	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS, Chromophobe Adenoma, Chromophobe Carcinoma, or Cystadenoma, NOS[b]	13/85 (15)	4/9 (44)B	21/46 (46)	20/43 (47)
P Values[c,d]	P < 0.001	N.S.	P < 0.001**	P < 0.001**
Relative Risk (Pooled Control)[f]			2.985	3.041
Lower Limit			1.581	1.601
Upper Limit			5.696	5.796
Relative Risk (Matched Control)[f]			1.027	1.047
Lower Limit			0.513	0.519
Upper Limit			3.432	3.493
Weeks to First Observed Tumor		103	102	77
Adrenal: Adenocarcinoma, NOS[b]	0/95 (0)	0/9 (0)	1/45 (2)	3/46 (7)
P Values[c,d]	P = 0.015	N.S.	N.S.	P = 0.033**
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.112	1.228
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.012	0.133
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	104	92

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Adenocarcinoma, NOS, or Cortical Adenoma[b]	3/95 (3)	1/9 (11)	4/45 (9)	10/46 (22)
P Values[c,d]	P < 0.001	N.S.	N.S.	P = 0.001**
Relative Risk (Pooled Control)[f]			2.815	6.884
Lower Limit			0.494	1.871
Upper Limit			18.356	36.913
Relative Risk (Matched Control)[f]			0.800	1.957
Lower Limit			0.099	0.358
Upper Limit			38.517	82.720
Weeks to First Observed Tumor		115	104	92
Thyroid: Follicular-cell Adenoma, Adenoma, NOS, or Cystadenoma[b]	7/86 (8)	1/9 (11)	10/44 (23)	12/43 (28)
P Values[c,d]	P = 0.002	N.S.	P = 0.022**	P = 0.004**
Relative Risk (Pooled Control)[f]			2.792	3.429
Lower Limit			1.026	1.340
Upper Limit			7.965	9.403
Relative Risk (Matched Control)[f]			2.045	2.512
Lower Limit			0.375	0.480
Upper Limit			86.341	104.131
Weeks to First Observed Tumor		115	68	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Adenocarcinoma, Cystadenocarcinoma, or Papillary Cystadenocarcinoma[b]	0/86 (0)	0/9 (0)	4/44 (9)	4/43 (9)
P Values[c,d]	P = 0.008	N.S.	P = 0.012**	P = 0.011**
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			1.794	1.836
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.215	0.220
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	104	115
Thyroid: All Follicular-cell Tumors[b,h]	7/86 (8)	1/9 (11)	14/44 (32)	14/43 (33)
P Values[c,d]	P < 0.001	N.S.	P = 0.001**	P = 0.001**
Relative Risk (Pooled Control)[f]			3.909	4.000
Lower Limit			1.596	1.635
Upper Limit			10.434	10.649
Relative Risk (Matched Control)[f]			2.864	2.930
Lower Limit			0.564	0.577
Upper Limit			117.305	119.913
Weeks to First Observed Tumor		115	68	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Parathyroid: Adenoma, NOS[b]	1/81 (1)	1/5 (20)[g]	0/26 (0)	4/24 (17)
P Values[c,d]	P = 0.004	N.S.	N.S.	P = 0.009**
Departure from Linear Trend[e]	P = 0.039	P = 0.042		
Relative Risk (Pooled Control)[f]			0.000	13.500
Lower Limit			0.000	1.403
Upper Limit			57.066	632.360
Relative Risk (Matched Control)[f]			0.000	0.833
Lower Limit			0.000	0.130
Upper Limit			3.557	39.161
Weeks to First Observed Tumor		107	--	113
All Sites: Hemangiosarcoma[b]	5/101 (5)	2/10 (20)[g]	0/50 (0)	5/49 (10)
P Values[c,d]	N.S.	N.S.	P = 0.025*(N)	N.S.
Departure fromLinear Trend[e]	P = 0.036	P = 0.006		
Relative Risk (Pooled Control)[f]			0.000	2.061
Lower Limit			0.000	0.494
Upper Limit			1.608	8.485
Relative Risk (Matched Control)[f]			0.000	0.510
Lower Limit			0.000	0.107
Upper Limit			0.667	5.008
Weeks to First Observed Tumor		89	--	71

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcoma or Hemangioma[b]	5/101 (5)	2/10 (20)[g]	1/50 (2)	6/49 (12)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]		P = 0.022		
Relative Risk (Pooled Control)[f]			0.404	2.473
Lower Limit			0.009	0.657
Upper Limit			3.459	9.689
Relative Risk (Matched Control)[f]			0.100	0.612
Lower Limit			0.002	0.141
Upper Limit			1.810	5.791
Weeks to First Observed Tumor		89	52	71
Pancreatic Islets: Islet-cell Adenoma[b]	2/92 (2)	0/9 (0)	1/47 (2)	4/45 (9)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.979	4.089
Lower Limit			0.017	0.607
Upper Limit			18.203	43.556
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.011	0.210
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	115	115

Table L1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma or Carcinoma[b]	2/92 (2)	0/9 (0)	1/47 (2)	6/45 (13)
P Values[c,d]	P = 0.008	P = 0.033	N.S.	P = 0.015**
Relative Risk (Pooled Control)[f]			0.979	6.133
Lower Limit			0.017	1.144
Upper Limit			18.203	59.753
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.011	0.363
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	115	97

[a]Dosed groups received 78 or 156 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when P < 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group (*) or the pooled-control group (**) when P < 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

[d]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each dosed group and the specified control group.

[g]The incidence in the matched-control group is significantly higher ($P < 0.05$) than that in the pooled controls (excluding the controls of the subject study).

[h]These tumors consist of adenoma, NOS, adenocarcinoma, NOS, follicular-cell adenoma, cystadenoma, NOS, cystadenocarcinoma, NOS, and papillary cystadenocarcinoma, NOS.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	6/104 (6)	2/9 (22)	2/47 (4)	5/45 (11)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.738	1.926
Lower Limit			0.074	0.485
Upper Limit			3.918	7.118
Relative Risk (Matched Control)[f]			0.191	0.500
Lower Limit			0.017	0.108
Upper Limit			2.467	4.871
Weeks to First Observed Tumor		115	110	95
Pituitary: Chromophobe Adenoma[b]	25/89 (28)	2/8 (25)	14/44 (32)	12/41 (29)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relaitve Risk (Pooled Control)[f]			1.133	1.042
Lower Limit			0.600	0.525
Upper Limit			2.001	1.901
Relative Risk (Matched Control)[f]			1.273	1.171
Lower Limit			0.411	0.366
Upper Limit			10.504	9.792
Weeks to First Observed Tumor		84	110	95

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary:				
Adenocarcinoma, NOS[b]	0/89 (0)	0/8 (0)	8/44 (18)	1/41 (2)
P Values[c,d]	N.S.	N.S.	P < 0.001**	N.S.
Departure from Linear Trend[e]	P < 0.001	P = 0.019		
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			4.572	0.115
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.481	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	98	99
Pituitary: Chromophobe Adenoma, Adenocarcinoma, NOS, Adenoma, or Cystadenoma, NOS[b]	29/89 (33)	2/8 (25)	22/44 (50)	15/41 (37)
P Values[c,d]	N.S.	N.S.	P = 0.040**	N.S.
Relative Risk (Pooled Control)[f]			1.534	1.123
Lower Limit			0.952	0.624
Upper Limit			2.360	1.882
Relative Risk (Matched Control)[f]			2.000	1.463
Lower Limit			0.693	0.479
Upper Limit			15.699	11.921
Weeks to First Observed Tumor		84	98	95

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Cortical Adenoma[b]	2/95 (2)	1/9 (11)	4/45 (9)	8/41 (20)
P Values[c,d]	P = 0.001	N.S.	N.S.	P = 0.001**
Relative Risk (Pooled Control)[f]			4.222	9.268
Lower Limit			0.626	1.944
Upper Limit			44.978	85.579
Relative Risk (Matched Control)[f]			0.800	1.756
Lower Limit			0.099	0.302
Upper Limit			38.517	75.723
Weeks to First Observed Tumor		75	115	115
Thyroid: Cystadenoma or Adenoma, NOS[b]	1/94 (1)	1/9 (11)g	6/45 (13)	4/38 (11)
P Values[c,d]	P = 0.010	N.S.	P = 0.005**	P = 0.024**
Relative Risk (Pooled Control)[f]			12.533	9.895
Lower Limit			1.580	1.014
Upper Limit			562.024	473.300
Relative Risk (Matched Control)[f]			1.200	0.947
Lower Limit			0.185	0.118
Upper Limit			53.895	45.380
Weeks to First Observed Tumor		115	98	75

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Adenocarcinoma, Cystadenocarcinoma, or Papillary Cystadenocarcinoma[b]	1/94 (1)	1/9 (11)g	2/45 (4)	1/38 (3)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			4.178	2.474
Lower Limit			0.222	0.032
Upper Limit			240.910	189.044
Relative Risk (Matched Control)[f]			0.400	0.237
Lower Limit			0.025	0.003
Upper Limit			23.103	18.138
Weeks to First Observed Tumor		115	115	115
Thyroid: All Follicular-cell Tumors[b,h]	2/94 (2)	2/9 (22)g	8/45 (18)	5/38 (13)
P Values[c,d]	P = 0.008	N.S.	P = 0.002**	P = 0.021**
Departure from Linear Trend[e]	P = 0.039			
Relative Risk (Pooled Control)[f]			8.356	6.184
Lower Limit			1.748	1.056
Upper Limit			77.514	62.055
Relative Risk (Matched Control)[f]			0.800	0.592
Lower Limit			0.214	0.129
Upper Limit			7.147	5.728
Weeks to First Observed Tumor		115	98	75

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dsoe
All Sites: Hemangioma or Hemangiosarcoma[a]	1/105 (1)	0/10 (0)	4/49 (8)	1/49 (2)
P Values[c,d]	N.S.	N.S.	P = 0.036**	N.S.
Departure from Linear Trend[e]	P = 0.018			
Relative Risk (Pooled Control)[f]			8.571	2.143
Lower Limit			0.973	0.028
Upper Limit			412.952	164.796
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.211	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	51	115
Mammary Gland: Adenocarcinoma, Cystadenocarcinoma, or Papillary Cystadenocarcinoma[b]	3/105 (3)	0/10 (0)	3/49 (6)	1/49 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			2.143	0.714
Lower Limit			0.295	0.014
Upper Limit			15.366	8.575
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.136	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	98	40

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma[b]	13/105 (12)	2/10 (20)	9/49 (18)	9/49 (18)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.484	1.484
Lower Limit			0.595	0.595
Upper Limit			3.456	3.456
Relative Risk (Matched Control)[f]			0.918	0.918
Lower Limit			0.247	0.247
Upper Limit			8.129	8.129
Weeks to First Observed Tumor		84	66	95
Uterus: Endometrial Stromal Polyp[b]	15/105 (14)	1/9 (11)	3/43 (7)	0/41 (0)
P Values[c,d]	P = 0.005(N)	N.S.	N.S.	P = 0.005**(N)
Relative Risk (Pooled Control)[f]			0.488	0.000
Lower Limit			0.094	0.000
Upper Limit			1.607	0.544
Relative Risk (Matched Control)[f]			0.628	0.000
Lower Limit			0.062	0.000
Upper Limit			32.213	4.097
Weeks to First Observed Tumor		84	80	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma[b]	5/97 (5)	2/7 (29)g	1/41 (2)	1/39 (3)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]		P = 0.015		
Relative Risk (Pooled Control)[f]			0.473	0.497
Lower Limit			0.010	0.011
Upper Limit			4.017	4.214
Relative Risk (Matched Control)[f]			0.085	0.090
Lower Limit			0.002	0.002
Upper Limit			1.513	1.588
Weeks to First Observed Tumor		115	115	115

[a]Dosed groups received 62.5 or 125 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when P < 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group (*) or with the pooled-control group (**) when P < 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

[d]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each dosed group and the specified control group.

[g]The incidence in the matched-control group is significantly higher ($P < 0.05$) than that in the pooled controls (excluding the controls of the subject study).

[h]These tumors consist of adenoma, NOS, adenocarcinoma, NOS, papillary adenocarcinoma, cystadenoma, NOS, and papillary cystadenocarcinoma, NOS.

Azinphos-methyl RIN: 7365-92

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TO: Judy Loranger

FROM: D. Ritter, TOX DUR 9-3-86

Subject: GUTHION Registration Standard.

In order to clarify the Oncogenic Effects portion of the RS for Toxicology I suggest that the following rewrite on p. 17 be included:

Para. II:

> "In an oncogenicity bioassay performed by the National Cancer Institute at Gulf Research Institute, azinphos-methyl was administered in the diet of Osborne-Mendel rats. Two groups of 50 male rats each received either 78 or 156 ppm for 80 weeks. Two groups of 50 females rats each received either 62.5 or 125 ppm for 80 weeks. Concurrent control groups consisted of 10 animals per sex each. All animals were observed for an additional 34 - 35 weeks. Neoplasms of the thyroid gland and of the pancreas suggested, but did not provide sufficient evidence to conclude, that azinphos methyl is oncogenic to male Osborne-Mendel rats. This study was judged to be inadequate for statistical evaluation of risk because only 10 concurrent control animals per sex were used".

Note:

In response to the question, "why were 10 control animals in this study not acceptable whereas 10 control animals was acceptable in the mouse study?":

The rat study showed evidence of potential oncogenicity and was subjected to Risk Analysis. Statistical techniques for this require that the numbers of control animals be at least similar to those in the treated group, which they were not. Hence, we asked for a new rat study.

The mouse study was clean for oncogenic effects; hence no Risk Analysis was needed. In any event, we consider that the mouse requirement is fulfilled.

CC:
Dr. Farber
Dr. Zendzian
Dr. Engler
Mr. Burnam
Mr. Jaeger

statistically, the association of the tumors in the adrenal is not well established. No such tumor is observed in female rats.

In male rats, the results of statistical tests using the pooled-control animals on the incidences of benign thyroid tumors (follicular-cell adenomas, adenomas, or cystadenomas), malignant thyroid tumors (adenocarcinomas, cystadenocarcinomas, or papillary cystadenocarcinomas), or the combined follicular-cell tumors are all significant. In each analysis, the result of the Cochran-Armitage test is significant ($P \leq 0.008$) using the pooled controls, and the results of the Fisher exact comparisons of the incidences in any of the dosed groups with the pooled-control group show probability levels less than 0.025. The results of the Fisher exact test comparing the incidence in the matched-control group with that in each dosed group are not significant. Time-adjusted analyses, eliminating animals that died before week 52 on study, were performed on the incidences of thyroid tumors. The analysis of time-adjusted data of 7/82 (9%) in the pooled-control group, 1/9 (11%) in the matched-control group, 14/44 (32%) in the low-dose group, and 14/43 (33%) in the high-dose group resulted in essentially the same statistics as those of the non-adjusted analysis. Since, however, the spontaneous incidence of these neoplasms varies in male Osborne-Mendel rats at this laboratory from 0% to 43%, with a

mean of 7%, the incidences found in low-dose or high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

In females, the results of the statistical tests on the combined incidence of the malignant thyroid tumors (adenocarcinomas, cystadenocarcinomas, or papillary cystadenocarcinomas) are not significant. The incidence in the matched controls does not differ statistically from that in the pooled controls. When the benign thyroid tumors are combined with the malignant tumors, the result of the Cochran-Armitage test on the combined incidence in female rats, using the pooled controls, is significant ($P = 0.008$), and the results of the Fisher exact test show that the incidences in the dosed groups are significantly higher (low-dose $P = 0.002$; high-dose $P = 0.021$) than that in the pooled controls. However, the incidence of 2/9 (22%) in the matched controls, higher than that of either dosed group, makes the significance seen in the use of the pooled controls questionable. Although the results of the statistical tests of the combined incidence of cystadenomas and adenomas in the thyroid are significant, the incidence seen in the matched controls is comparable to those in the dosed groups.

When the the number of female rats with some type of pituitary tumor (chromophobe adenomas, adenocarcinomas, adenomas, or

cystadenomas) are analyzed, the results of the Cochran-Armitage test are not significant, and the Fisher exact comparison of incidences in the low-dose and pooled-control groups indicates a probability level of 0.040, which is above the 0.025 level required by the Bonferroni inequality criterion when multiple comparison is considered. The incidence in the high-dose group is not significant.

In female rats, when hemangiomas and hemangiosarcomas are grouped for analysis, the results of the Cochran-Armitage test are not significant, but an indicated departure from linear trend is observed (P = 0.018), using the pooled controls, since the incidence in the low-dose group is greater than that in the high-dose group. The Fisher exact comparison of the incidences in the low-dose and pooled-control groups indicates a probability level of 0.036, which is above the 0.025 level required by the Bonferroni inequality criterion when multiple comparison is considered. The incidence in the high-dose group is not significant. The incidence of these tumors in the male rats is not significant.

Some incidences at specific tumor sites indicate a higher incidence in the matched controls than in the pooled controls (marked "g" in the tables) or a comparable or higher incidence in the matched controls than in the dosed groups. Under these

circumstances, the significance generated by the use of the pooled controls is questionable. The tumors which are not said to be dose associated, because of these reasons, are the pituitary tumors, the parathyroid tumors, and hemangiomas or hemangiosarcomas in male rats; along with the liver tumors, cortical adenomas in the adrenal, fibroadenomas of the mammary gland, tumors of the uterus, and tumors of the pancreatic islet in female rats.

In summary, the statistical tests suggest that the incidences of thyroid and pancreatic islet-cell tumors in male rats are associated with administration of azinphosmethyl. None of the tumors in females could be associated with the test chemical.

V. DISCUSSION

In this bioassay, azinphosmethyl had a toxic effect on both rats and mice, as demonstrated by depressed mean body weights, clinical signs, and/or lower survival. High- and low-dose male rats, high-dose female rats, and high-dose female mice had lower mean body weights than their corresponding controls throughout the study. Typical signs of organophosphorus intoxication were present in a few animals of both species and included hyperactivity, tremors, and dyspnea. Convulsions in the mice may have been related to organophosphorus intoxication, although they were also seen in one control male mouse. In male rats and in both male and female mice, tests for dose-related trends in mortality over the bioassay were not significant at the 0.05 level. In female rats, 50% of the high-dose animals survived until the end of the bioassay, compared with 68% of the low-dose animals and 70% of the controls. Sufficient numbers of animals were at risk in each species for development of late-appearing tumors.

A great many tumors of the endocrine organs were observed in both dosed male and female rats but the small size of the matched control groups made interpretation difficult. Those of the adrenal in dosed males and females, the follicular cells of the thyroid in dosed males and females, the anterior pituitary in dosed males, and the parathyroid in dosed males occurred at

statistically significant incidences when compared with pooled controls, but not with matched controls. Since the pathologist examining the dosed and matched-control animals did not examine the pooled controls, and since the incidences of the pituitary and parathyroid in males, and of the thyroid in females were significantly higher in the matched controls than in the pooled controls, these neoplasms cannot be clearly related to administration of azinphosmethyl. The incidence of adenocarcinoma of the pituitary in female rats cannot be clearly associated with administration of the test chemical, since the dose-related trend and the incidence of tumors in the high-dose group were not significant; also, the combined benign and malignant tumors of the pituitary occurred at a lower level of significance than the adenocarcinoma alone. Although the incidence of tumors of the liver showed a dose-related trend in the male rats, the incidences in the dosed groups were not significantly higher than those in the controls, and these tumors cannot, therefore, be clearly related to administration of the test chemical.

In male rats, islet-cell adenomas or carcinomas of the pancreas occurred at a significant incidence ($P = 0.015$) in the high-dose male rats when compared with pooled controls (pooled controls 2/92, matched controls 0/9, low-dose 1/47, high-dose 6/45), and

the incidences showed a dose-related trend (P = 0.008), using the pooled controls. Two of the high-dose males had carcinomas, while the remaining four had adenomas. Since, however, the spontaneous incidence of this lesion varies in male Osborne-Mendel rats at this laboratory from 0% to 22%, with a mean of 2%, the incidence found in the high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

Follicular-cell tumors of the thyroid, either benign (adenomas, follicular-cell adenomas, or cystadenomas), malignant (adenocarcinomas, cystadenocarcinomas, or papillary cystadenocarcinomas), or combined benign and malignant occurred at significant incidences in dosed male rats when compared with pooled controls; the combined tumors occurred at significant incidences (P = 0.001) in both low- and high-dose groups when compared with pooled controls (pooled controls 7/86, matched controls 1/9, low-dose 14/44, high-dose 14/43), and the incidences showed a dose-related trend (P < 0.001), using the pooled controls. Since, however, the spontaneous incidence of these neoplasms varies in male Osborne-Mendel rats at this laboratory from 0% to 43%, with a mean of 7%, the incidences found in low-dose or high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

In mice, hepatocellular adenomas or carcinomas occurred at a significant incidence (P = 0.040) in the high-dose male mice when compared with pooled controls (pooled controls 30/128, matched controls 2/3, low-dose 11/49, high-dose 19/50), and the incidences showed a dose-related trend (P = 0.048). Hepatocellular adenomas and carcinomas were diagnosed among the dosed and matched-control groups, and neoplastic nodules of the liver were diagnosed in addition in animals of the pooled-control group. The probability level of the liver tumors in the high-dose group is above that required for significance using the Bonferroni inequality criterion for multiple comparisons, and similar high incidences have been noted in other groups of controls at the same laboratory; thus, these liver tumors in male mice are not considered to be related to administration of the test chemical.

Azinphosmethyl is an organophosphorus chemical with a primary biological action of inhibiting acetylcholinesterase. This activity was very low when serum, homogenized brain, or submaxillary gland were tested in vitro; however, the chemical is rapidly oxidized in vivo to the active chemical (DuBois et al., 1957). In a 2-year feeding study using Wistar rats, there was no indication that administration of the chemical at concentrations up to 50-100 ppm induced tumors (Worden et al., 1973). This

concentration was comparable to that fed to the low-dose rats in the present study.

It is concluded that under the conditions of this bioassay, neoplasms of the thyroid and pancreatic islets suggest but do not provide sufficient evidence for carcinogenicity of azinphosmethyl in male Osborne-Mendel rats. Azinphosmethyl was not shown to be carcinogenic in female Osborne-Mendel rats or in B6C3F1 mice of either sex.

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma[b]	5/101 (5)	1/10 (10)	3/50 (6)	1/49 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.212	0.412
Lower Limit			0.194	0.009
Upper Limit			5.931	3.527
Relative Risk (Matched Control)[f]			0.600	0.204
Lower Limit			0.058	0.003
Upper Limit			30.890	15.723
Weeks to First Observed Tumor		115	68	113
Liver: Hepatocellular Adenoma[b]	3/99 (3)	1/9 (11)	3/49 (6)	5/46 (11)
P Values[c,d]	P = 0.044	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			2.020	3.587
Lower Limit			0.278	0.726
Upper Limit			14.484	22.059
Relative Risk (Matched Control)[f]			0.551	0.978
Lower Limit			0.055	0.139
Upper Limit			28.360	45.235
Weeks to First Observed Tumor		115	115	97

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	13/85 (15)	4/9 (44)[g]	21/46 (46)	13/43 (30)
P Values[c,d]	P = 0.012	N.S.	P < 0.001**	P = 0.042**
Departure from Linear Trend[e]	P = 0.004			
Relative Risk (Pooled Control)[f]			2.985	1.977
Lower Limit			1.581	0.920
Upper Limit			5.696	4.147
Relative Risk (Matched Control)[f]			1.027	0.680
Lower Limit			0.513	0.312
Upper Limit			3.432	2.420
Weeks to First Observed Tumor		103	102	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	13/85 (15)	4/9 (44)[g]	21/46 (46)	15/43 (35)
P Values[c,d]	P = 0.003	N.S.	P < 0.001**	P = 0.012**
Departure from Linear Trend[e]	P = 0.009			
Relative Risk (Pooled Control)[f]			2.985	2.281
Lower Limit			1.581	1.110
Upper Limit			5.696	4.634
Relative Risk (Matched Control)[f]			1.027	0.785
Lower Limit			0.513	0.371
Upper Limit			3.432	2.733
Weeks to First Observed Tumor		103	102	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS, Chromophobe Adenoma, Chromophobe Carcinoma, or Cystadenoma, NOS[b]	13/85 (15)	4/9 (44)[B]	21/46 (46)	20/43 (47)
P Values[c,d]	P < 0.001	N.S.	P < 0.001**	P < 0.001**
Relaive Risk (Pooled Control)[f]			2.985	3.041
Lower Limit			1.581	1.601
Upper Limit			5.696	5.796
Relative Risk (Matched Control)[f]			1.027	1.047
Lower Limit			0.513	0.519
Upper Limit			3.432	3.493
Weeks to First Observed Tumor		103	102	77
Adrenal: Adenocarcinoma, NOS[b]	0/95 (0)	0/9 (0)	1/45 (2)	3/46 (7)
P Values[c,d]	P = 0.015	N.S.	N.S.	P = 0.033**
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.112	1.228
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.012	0.133
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	104	92

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Adenocarcinoma, NOS, or Cortical Adenoma[b]	3/95 (3)	1/9 (11)	4/45 (9)	10/46 (22)
P Values[c,d]	P < 0.001	N.S.	N.S.	P = 0.001**
Relative Risk (Pooled Control)[f]			2.815	6.884
Lower Limit			0.494	1.871
Upper Limit			18.356	36.913
Relative Risk (Matched Control)[f]			0.800	1.957
Lower Limit			0.099	0.358
Upper Limit			38.517	82.720
Weeks to First Observed Tumor		115	104	92
Thyroid: Follicular-cell Adenoma, Adenoma, NOS, or Cystadenoma[b]	7/86 (8)	1/9 (11)	10/44 (23)	12/43 (28)
P Values[c,d]	P = 0.002	N.S.	P = 0.022**	P = 0.004**
Relative Risk (Pooled Control)[f]			2.792	3.429
Lower Limit			1.026	1.340
Upper Limit			7.965	9.403
Relative Risk (Matched Control)[f]			2.045	2.512
Lower Limit			0.375	0.480
Upper Limit			86.341	104.131
Weeks to First Observed Tumor		115	68	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Adenocarcinoma, Cystadenocarcinoma, or Papillary Cystadenocarcinoma[b]	0/86 (0)	0/9 (0)	4/44 (9)	4/43 (9)
P Values[c,d]	P = 0.008	N.S.	P = 0.012**	P = 0.011**
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			1.794	1.836
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.215	0.220
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	104	115
Thyroid: All Follicular-cell Tumors[b,h]	7/86 (8)	1/9 (11)	14/44 (32)	14/43 (33)
P Values[c,d]	P < 0.001	N.S.	P = 0.001**	P = 0.001**
Relative Risk (Pooled Control)[f]			3.909	4.000
Lower Limit			1.596	1.635
Upper Limit			10.434	10.649
Relative Risk (Matched Control)[f]			2.864	2.930
Lower Limit			0.564	0.577
Upper Limit			117.305	119.913
Weeks to First Observed Tumor		115	68	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Parathyroid: Adenoma, NOS[b]	1/81 (1)	1/5 (20)[g]	0/26 (0)	4/24 (17)
P Values[c,d]	P = 0.004	N.S.	N.S.	P = 0.009**
Departure from Linear Trend[e]	P = 0.039	P = 0.042		
Relative Risk (Pooled Control)[f]			0.000	13.500
Lower Limit			0.000	1.403
Upper Limit			57.066	632.360
Relative Risk (Matched Control)[f]			0.000	0.833
Lower Limit			0.000	0.130
Upper Limit			3.557	39.161
Weeks to First Observed Tumor		107	--	113
All Sites: Hemangiosarcoma[b]	5/101 (5)	2/10 (20)[g]	0/50 (0)	5/49 (10)
P Values[c,d]	N.S.	N.S.	P = 0.025*(N)	N.S.
Departure fromLinear Trend[e]	P = 0.036	P = 0.006		
Relative Risk (Pooled Control)[f]			0.000	2.061
Lower Limit			0.000	0.494
Upper Limit			1.608	8.485
Relative Risk (Matched Control)[f]			0.000	0.510
Lower Limit			0.000	0.107
Upper Limit			0.667	5.008
Weeks to First Observed Tumor		89	--	71

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcoma or Hemangioma[b]	5/101 (5)	2/10 (20)g	1/50 (2)	6/49 (12)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]		P = 0.022		
Relative Risk (Pooled Control)[f]			0.404	2.473
Lower Limit			0.009	0.657
Upper Limit			3.459	9.689
Relative Risk (Matched Control)[f]			0.100	0.612
Lower Limit			0.002	0.141
Upper Limit			1.810	5.791
Weeks to First Observed Tumor		89	52	71
Pancreatic Islets: Islet-cell Adenoma[b]	2/92 (2)	0/9 (0)	1/47 (2)	4/45 (9)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.979	4.089
Lower Limit			0.017	0.607
Upper Limit			18.203	43.556
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.011	0.210
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	115	115

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma or Carcinoma[b]	2/92 (2)	0/9 (0)	1/47 (2)	6/45 (13)
P Values[c,d]	P = 0.008	P = 0.033	N.S.	P = 0.015**
Relative Risk (Pooled Control)[f]			0.979	6.133
Lower Limit			0.017	1.144
Upper Limit			18.203	59.753
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.011	0.363
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	115	97

[a]Dosed groups received 78 or 156 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when P < 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the [illegible] test for the comparison of that dosed group with the matched-control group (*) or [illegible] pooled-control group (**) when P < 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

[d]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each dosed group and the specified control group.

[g]The incidence in the matched-control group is significantly higher ($P < 0.05$) than that in the pooled controls (excluding the controls of the subject study).

[h]These tumors consist of adenoma, NOS, adenocarcinoma, NOS, follicular-cell adenoma, cystadenoma, NOS, cystadenocarcinoma, NOS, and papillary cystadenocarcinoma, NOS.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	6/104 (6)	2/9 (22)	2/47 (4)	5/45 (11)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.738	1.926
Lower Limit			0.074	0.485
Upper Limit			3.918	7.118
Relative Risk (Matched Control)[f]			0.191	0.500
Lower Limit			0.017	0.108
Upper Limit			2.467	4.871
Weeks to First Observed Tumor		115	110	95
Pituitary: Chromophobe Adenoma[b]	25/89 (28)	2/8 (25)	14/44 (32)	12/41 (29)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relaitve Risk (Pooled Control)[f]			1.133	1.042
Lower Limit			0.600	0.525
Upper Limit			2.001	1.901
Relative Risk (Matched Control)[f]			1.273	1.171
Lower Limit			0.411	0.366
Upper Limit			10.504	9.792
Weeks to First Observed Tumor		84	110	95

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary:				
Adenocarcinoma, NOS[b]	0/89 (0)	0/8 (0)	8/44 (18)	1/41 (2)
P Values[c,d]	N.S.	N.S.	P < 0.001**	N.S.
Departure from Linear Trend[e]	P < 0.001	P = 0.019		
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			4.572	0.115
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.481	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	98	99
Pituitary: Chromophobe Adenoma, Adenocarcinoma, NOS, Adenoma, or Cystadenoma, NOS[b]	29/89 (33)	2/8 (25)	22/44 (50)	15/41 (37)
P Values[c,d]	N.S.	N.S.	P = 0.040**	N.S.
Relative Risk (Pooled Control)[f]			1.534	1.123
Lower Limit			0.952	0.624
Upper Limit			2.360	1.882
Relative Risk (Matched Control)[f]			2.000	1.463
Lower Limit			0.693	0.479
Upper Limit			15.699	11.921
Weeks to First Observed Tumor		84	98	95

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Cortical Adenoma[b]	2/95 (2)	1/9 (11)	4/45 (9)	8/41 (20)
P Values[c,d]	P = 0.001	N.S.	N.S.	P = 0.001**
Relative Risk (Pooled Control)[f]			4.222	9.268
Lower Limit			0.626	1.944
Upper Limit			44.978	85.579
Relative Risk (Matched Control)[f]			0.800	1.756
Lower Limit			0.099	0.302
Upper Limit			38.517	75.723
Weeks to First Observed Tumor		75	115	115
Thyroid: Cystadenoma or Adenoma, NOS[b]	1/94 (1)	1/9 (11)8	6/45 (13)	4/38 (11)
P Values[c,d]	P = 0.010	N.S.	P = 0.005**	P = 0.024**
Relative Risk (Pooled Control)[f]			12.533	9.895
Lower Limit			1.580	1.014
Upper Limit			562.024	473.300
Relative Risk (Matched Control)[f]			1.200	0.947
Lower Limit			0.185	0.118
Upper Limit			53.895	45.380
Weeks to First Observed Tumor		115	98	75

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Adenocarcinoma, Cystadenocarcinoma, or Papillary Cystadenocarcinoma[b]	1/94 (1)	1/9 (11)g	2/45 (4)	1/38 (3)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			4.178	2.474
Lower Limit			0.222	0.032
Upper Limit			240.910	189.044
Relative Risk (Matched Control)[f]			0.400	0.237
Lower Limit			0.025	0.003
Upper Limit			23.103	18.138
Weeks to First Observed Tumor		115	115	115
Thyroid: All Follicular-cell Tumors[b,h]	2/94 (2)	2/9 (22)g	8/45 (18)	5/38 (13)
P Values[c,d]	P = 0.008	N.S.	P = 0.002**	P = 0.021**
Departure from Linear Trend[e]	P = 0.039			
Relative Risk (Pooled Control)[f]			8.356	6.184
Lower Limit			1.748	1.056
Upper Limit			77.514	62.055
Relative Risk (Matched Control)[f]			0.800	0.592
Lower Limit			0.214	0.129
Upper Limit			7.147	5.728
Weeks to First Observed Tumor		115	98	75

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dsoe
All Sites: Hemangioma or Hemangiosarcoma[a]	1/105 (1)	0/10 (0)	4/49 (8)	1/49 (2)
P Values[c,d]	N.S.	N.S.	P = 0.036**	N.S.
Departure from Linear Trend[e]	P = 0.018			
Relative Risk (Pooled Control)[f]			8.571	2.143
Lower Limit			0.873	0.028
Upper Limit			412.952	164.796
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.211	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	51	115
Mammary Gland: Adenocarcinoma, Cystadenocarcinoma, or Papillary Cystadenocarcinoma[b]	3/105 (3)	0/10 (0)	3/49 (6)	1/49 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			2.143	0.714
Lower Limit			0.295	0.014
Upper Limit			15.366	8.575
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.136	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	98	40

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma[b]	13/105 (12)	2/10 (20)	9/49 (18)	9/49 (18)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.484	1.484
Lower Limit			0.595	0.595
Upper Limit			3.456	3.456
Relative Risk (Matched Control)[f]			0.918	0.918
Lower Limit			0.247	0.247
Upper Limit			8.129	8.129
Weeks to First Observed Tumor		84	66	95
Uterus: Endometrial Stromal Polyp[b]	15/105 (14)	1/9 (11)	3/43 (7)	0/41 (0)
P Values[c,d]	P = 0.005(N)	N.S.	N.S.	P = 0.005**(N)
Relative Risk (Pooled Control)[f]			0.488	0.000
Lower Limit			0.094	0.000
Upper Limit			1.607	0.544
Relative Risk (Matched Control)[f]			0.628	0.000
Lower Limit			0.062	0.000
Upper Limit			32.213	4.097
Weeks to First Observed Tumor		84	80	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma[b]	5/97 (5)	2/7 (29)[g]	1/41 (2)	1/39 (3)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]		P = 0.015		
Relative Risk (Pooled Control)[f]			0.473	0.497
Lower Limit			0.010	0.011
Upper Limit			4.017	4.214
Relative Risk (Matched Control)[f]			0.085	0.090
Lower Limit			0.002	0.002
Upper Limit			1.513	1.588
Weeks to First Observed Tumor		115	115	115

[a]Dosed groups received 62.5 or 125 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when P < 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group (*) or with the pooled-control group (**) when P < 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

[d]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each dosed group and the specified control group.

[g]The incidence in the matched-control group is significantly higher ($P < 0.05$) than that in the pooled controls (excluding the controls of the subject study).

[h]These tumors consist of adenoma, NOS, adenocarcinoma, NOS, papillary adenocarcinoma, cystadenoma, NOS, and papillary cystadenocarcinoma, NOS.

Azinphos-methyl RIN: 7365-92

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Pages 49 through 88 are not included.

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____ Description of quality control procedures.

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____ Sales or other commercial/financial information.

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TO: Judy Loranger

FROM: D. Ritter, TOX 042 9-3-86

Subject: GUTHION Registration Standard.

In order to clarify the Oncogenic Effects portion of the RS for Toxicology I suggest that the following rewrite on p. 17 be included:

Para. II:

> "In an oncogenicity bioassay performed by the National Cancer Institute at Gulf Research Institute, azinphos-methyl was administered in the diet of Osborne-Mendel rats. Two groups of 50 male rats each received either 78 or 156 ppm for 80 weeks. Two groups of 50 females rats each received either 62.5 or 125 ppm for 80 weeks. Concurrent control groups consisted of 10 animals per sex each. All animals were observed for an additional 34 - 35 weeks. Neoplasms of the thyroid gland and of the pancreas suggested, but did not provide sufficient evidence to conclude, that azinphos methyl is oncogenic to male Osborne-Mendel rats. This study was judged to be inadequate for statistical evaluation of risk because only 10 concurrent control animals per sex were used".

Note:

In response to the question, "why were 10 control animals in this study not acceptable whereas 10 control animals was acceptable in the mouse study?":

The rat study showed evidence of potential oncogenicity and was subjected to Risk Analysis. Statistical techniques for this require that the numbers of control animals be at least similar to those in the treated group, which they were not. Hence, we asked for a new rat study.

The mouse study was clean for oncogenic effects; hence no Risk Analysis was needed. In any event, we consider that the mouse requirement is fulfilled.

CC:
Dr. Farber
Dr. Zendzian
Dr. Engler
Mr. Burnam
Mr. Jaeger