



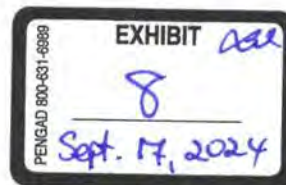
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUMMARY OF THE IBT REVIEW PROGRAM

OFFICE OF PESTICIDE PROGRAMS

JULY 1983



Case ID: 220300429
Control No.: 26064959



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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

The IBT Review Program

This report summarizes the findings of the joint program conducted by the Environmental Protection Agency (EPA) and the Health Protection Branch of Health and Welfare Canada to reexamine the validity of health effects studies on pesticides tested by Industrial Bio-Test Laboratories, Inc. (IBT). This program is one result of discoveries made during a series of audits beginning in 1976 by the Food and Drug Administration (FDA) and EPA which revealed serious deficiencies in IBT tests conducted to support the registration of numerous pesticides and some drugs in both the United States and Canada. This report assesses the impact of the IBT situation on the registration status of the chemicals involved and describes the steps the Agency has taken to resolve this problem and to prevent its recurrence.

Exhibit A shows how many IBT and non-IBT tests are available to EPA in each testing category for the pesticide chemicals having some IBT conducted studies in their data base. As these tables show, a large majority (93%) of the pesticides tested by IBT, also have non-IBT data available. Only 12 of the pesticides listed have a data base entirely of IBT studies. However, seven of these are either not registered for use in this country or are cancelled or discontinued products. Some of the IBT studies on the remaining five chemicals are at least partially valid or "supplemental", meaning the data can be used to support the findings of other studies.

These tables also indicate the pesticides for which new data have been required as a result of EPA regulatory actions. These include risk/benefit reviews undertaken because of specific evidence of a hazard (known as Rebuttable Presumption Against Registration, listed as "RPAR" in tables) or EPA's regular program for reregistering all previously registered pesticides (in tables, "Registration Standard" and "Data Call-In"). The reregistration program is not specifically connected to the IBT case, but serves the purpose of bringing the data on older chemicals, including some tested by IBT, up to current scientific standards. Under the authority of section 3(c)(2)(B) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) the Agency can require additional data to maintain a registration, and may suspend a product's registration if the registrant does not agree to provide the data or if it is not provided pursuant to an agreement with the Agency.

Attached is also a list (Exhibit B) of major health effects studies on pesticides conducted by IBT identifying which have been found valid or invalid, and which have been or are in the process of being replaced. This list covers 801 studies on 140 pesticides. An earlier draft list of IBT tests prepared by EPA in May 1983 identified 1205 tests on 212 pesticides. The current list has eliminated duplicative entries, preliminary range finding and similar tests which were not true health effects studies, and short-term, acute toxicity tests which generally do not create a significant data gap and which will be replaced if needed, through the existing reregistration program described above. Thus, the current list of 801 studies covers health effects considered significant to regulatory decisions, such as induction of benign or malignant tumors (oncogenicity), birth defects (teratogenicity), genetic mutations, other adverse reproductive effects, and neurotoxicity. Of the 801 IBT studies in the pivotal categories, 594 (74%) have been found invalid. To date, of the invalid studies, 212 (36%) studies have been replaced or are in progress, 38 (7%) are under discussion for possible replacement, and 45 (7%) are of a type no longer required for registration.

One way to assess the impact of IBT is to consider the effect of invalid studies on the data base supporting pesticides used in high volume. Although hundreds of pesticides are registered, only 25 insecticides account for 85% of the actual pounds of insecticides used, 32 herbicides account for 82%, and only 8 fungicides account for 71% of the volume of those products used. Of these 65 most heavily used pesticides, only 18 have IBT data in one or

more important categories. Of those 18, all but one also have non-IBT data available in some or all of the same categories. The exception, prometon, a herbicide not used on food crops, has one partially valid IBT study and many non-IBT acute and subacute studies. Sixteen of these high volume chemicals are the subject of one of the regulatory procedures described above requiring additional data. Thus, the data bases for the high volume chemicals to which people are most likely to be exposed are for the most part unaffected by the IBT situation, and where there is an impact, EPA has taken active regulatory steps to obtain replacement data.

The principal remaining task of the IBT program is to clarify the status of the invalid studies for which registrants have indicated they do not intend to provide replacements, or have not communicated an intention one way or the other to EPA. Although around 300 studies are in this category, a significant number (140) of negative and non-responses involve discontinued or cancelled products, or pesticides of such low volume use that registrants may choose not to invest in further testing needed to maintain registrations. The replacement status column of Exhibit B indicates that there are 159 invalid studies (26% of invalid IBT tests) for which there is negative or no response. However, as previously noted, most of these chemicals have non-IBT data available. Exhibit A shows that only five chemicals still registered and actually used have entirely IBT data bases. The 17 studies involved with those 5 chemicals constitute 3% of invalid IBT studies. A registration standard will result in replacement of 6 of these studies. This leaves only 11 studies or 2% of the invalid IBT tests which constitute the sole support of registered pesticides, and for which no regulatory action to generate replacement data has yet been initiated. Several of these 11 are valid or have at least supplementary value.

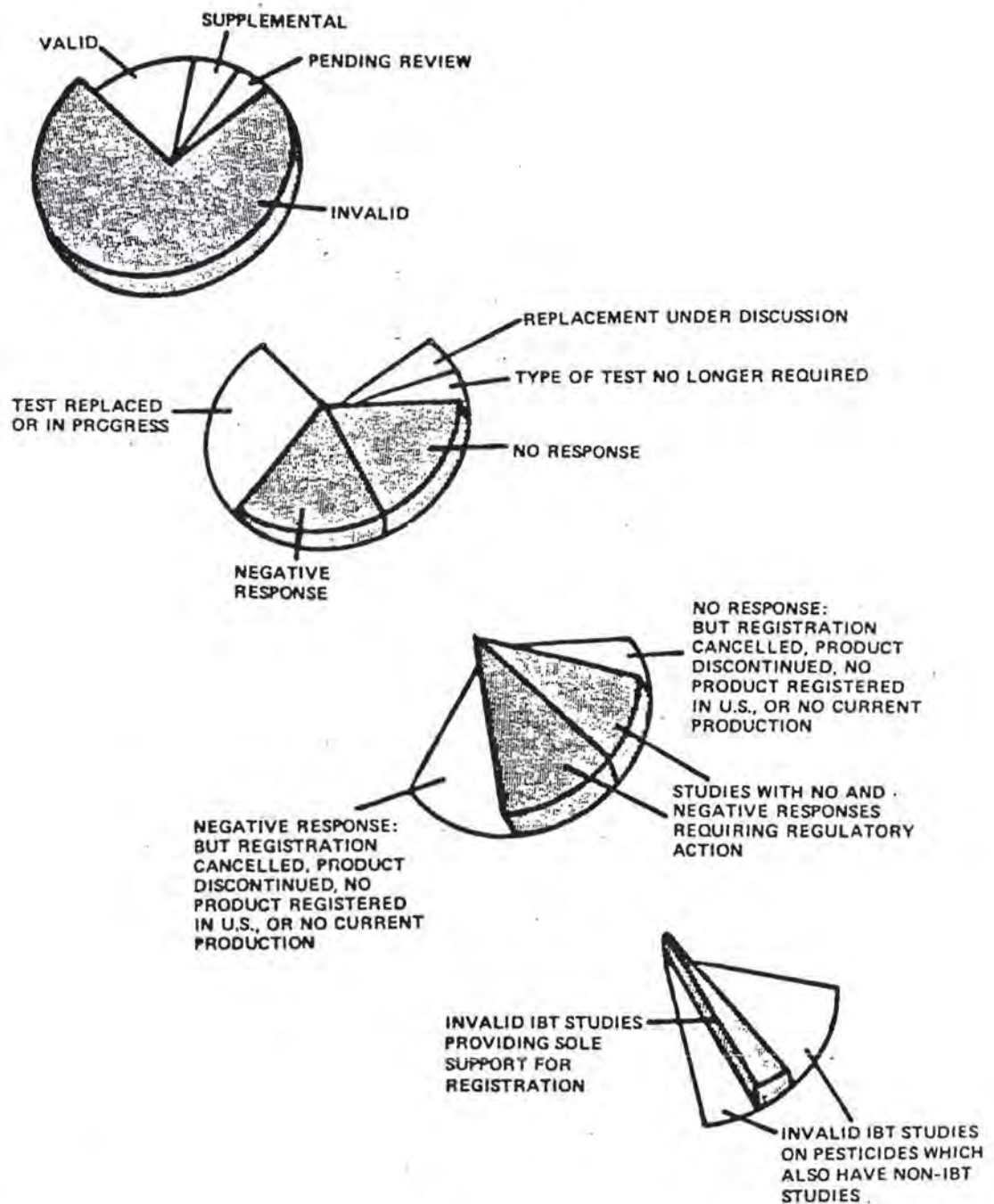
This report is being furnished to the registrants of the affected chemicals for which negative or no responses have been received concerning replacement of invalid IBT studies. We are also sending the registrants 3(c)(2)(B) notifications which require a registrant to make a specific commitment within 90 days or the registration may be suspended. In some cases, EPA and a registrant may agree that a specific study does not need to be replaced.

The IBT case caused serious concern and uncertainty about the potential hazards of the hundreds of pesticides involved, both for EPA and the public. Although it was advocated by some that all 212 pesticides tested in whole or in part by IBT be removed from the market pending retesting, that option is not available under current law.

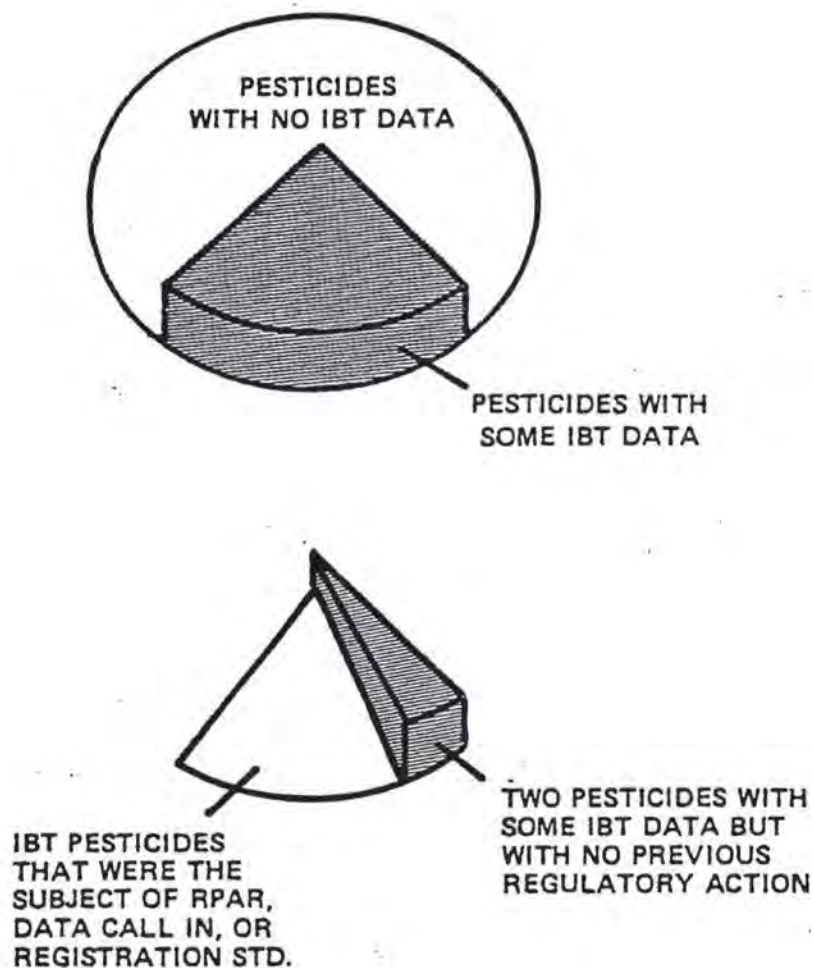
The regulatory response authorized by FIFRA requires valid evidence of risk, as opposed to a lack of information, before removing a product from the market, and allows for the replacement of inadequate data. As we reach the final resolution of the IBT problem, it appears that this approach was appropriate and adequate to deal with this event.

The IBT scandal shook the industry and government regulators. Obviously, steps had to be taken, not just to deal with the IBT situation itself, but to ensure that data providing the foundation of regulatory decisions in the future are adequately prepared and scrutinized. Thus, another result of the IBT case was the establishment in 1977 of a joint EPA-FDA audit program to help ensure that another IBT situation has not occurred and will not in the future. The lab audit program includes visits to laboratories to inspect their procedures, facilities and staff qualifications, and about sixty audits per year of labs and/or individual pesticide studies to see if the reported results are supported by the "raw" laboratory records and data. In the past six years, we have found the large majority of laboratories to be in compliance with current standards, and producing scientifically valid studies. An important effect of the IBT case has been to make the testing community, the industries which use their services, and government regulators keenly aware of the need to maintain high standards of quality control over health effects testing.

EPA ASSESSMENT OF THE 801 MAJOR IBT TESTS



EPA ASSESSMENT OF EFFECT OF IBT DATA ON 65 LARGEST USE PESTICIDES *



*25 INSECTICIDES ACCOUNTING FOR 85% OF POUNDAGE USED,
32 HERBICIDES ACCOUNTING FOR 82% OF POUNDAGE USED,
AND 8 FUNGICIDES ACCOUNTING FOR 71% OF POUNDAGE USED,
IN 1980.

SUMMARY STATISTICS: IBT

TOTALS

38 COMPANIES
140 CHEMICALS
801 STUDIES

STUDY VALIDATION STATUS

131 16% VALID
44 6% SUPPLEMENTAL
32 4% PENDING
594 74% INVALID
801 100%

INVALID STUDY REPLACEMENT STATUS

212 36% STUDY REPLACED OR IN PROGRESS
38 6% REPLACEMENT UNDER DISCUSSION
45 8% STUDY NO LONGER REQUIRED
116 20% NEGATIVE RESPONSE BUT PRODUCTS ARE CANCELLED,
DISCONTINUED, NOT REGISTERED IN THE U.S., OR HAVE
NO PRODUCTION.
24 4% NO RESPONSE BUT PRODUCTS ARE CANCELLED, DISCONTINUED
NOT REGISTERED IN THE U.S., OR HAVE NO PRODUCTION.
86 14% NEGATIVE RESPONSE AND INVALID
73 12% NO RESPONSE AND INVALID
594 100%

IBT STUDIES PROVIDING SOLE SUPPORT FOR REGISTRATION

17 3% IBT STUDIES PROVIDE SOLE SUPPORT FOR REGISTRATION
-6 1% CHRONIC STUDIES GENERATED BY REGISTRATION STANDARD
11 2%



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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

ADDITIONAL BACKGROUND ON THE IBT REVIEW PROGRAM

In 1976, during a routine lab inspection of one of IBT's facilities, FDA discovered deficiencies in the manner in which studies were being conducted and discrepancies between those studies and their raw data. In 1977, EPA placed a moratorium on registration actions involving data developed at IBT as a result of this information. In the same year, EPA notified registrants that they were required to audit the raw data and validate both those IBT studies which were pivotal to the data base of pesticides already registered and all those which were supporting new registration actions.

In 1978 a joint EPA/FDA audit of IBT's two other facilities uncovered problems similar to those discovered during the initial audit. In March of that year EPA required registrants to submit to EPA the raw data for the IBT studies so that a review of registrant audits could be conducted.

EPA referred this case to the Department of Justice for investigation in April 1978. At approximately the same time, the U.S. and Canada were negotiating an agreement to share the task of spot checking registrants' audits of IBT studies. Through these checks, however, it became apparent that registrants' audits routinely overlooked some areas of concern. As a result, Canada and the U.S. agreed to review each audit and study.

Mutual agreement was reached as to which studies would be reviewed by each country. It was also decided that each country would accept the other's determination as to validity. However, due to differences in data requirements, each country would independently evaluate whether studies met their regulatory requirements, and determine the need for replacement studies.

After two years experience of the review program a decision was made to reconsider past policies regarding IBT data. A policy statement reflecting decisions made as a result of this analysis was sent to registrants in July 1980. The decisions were: 1) that the moratorium on registration actions was lifted unless a valid IBT study was essential to the approval of a specific action, 2) that registrants would be required to fill data gaps resulting from invalid IBT studies, 3) minor data gaps would be considered through normal registration channels, 4) if the entire data base was invalid, EPA would consider cancellation action, and 5) if previously unreported adverse effects were discovered, the study would have to be replaced, and in addition the Agency would consider initiating either an intensive risk/benefit review, or formal hearings on a chemical's registration status.

The IBT Review Program consisted of validation review, evaluation review, and data gap review. Validation review was designed to determine whether the information in the final report was supported by the raw data. Evaluation of whether a study met Agency guidelines for studies used to support registration, was performed on studies determined to be valid or at least reliable enough to supplement other valid data. Data gap review was a search through a chemical's entire data base to determine which invalid studies needed to be replaced.

Because our experience with data gap review proved it to be extremely time consuming, options for completing the IBT program more expeditiously were considered. As a result, several policy changes were adopted and conveyed to registrants in a letter in April 1982 which stated: 1) that acute IBT studies would no longer be reviewed through the IBT program. Instead, they would be reviewed through normal registration channels; 2) that studies which were considered invalid because the registrant initially chose not to audit them, would not be reviewed by the Agency and our presumption would be that they had to be replaced; 3) that EPA would no longer perform a data gap review of a chemical's data base to determine if other studies existed to replace the IBT studies, instead we would assume that replacement was necessary unless the registrant could convince us otherwise; and 4) that EPA would not review an IBT study if the registrant identified a replacement and agreed to have the IBT study considered invalid.

The review stage of the IBT program is essentially complete. The remainder of the program consists of obtaining replacement studies and tracking commitments to replace studies.

EXHIBIT A

THE DATA BASE FOR INDUSTRIAL BIO-TEST CHEMICALS

Exhibit A quantitatively presents the data base of the chemical compounds for which studies were conducted by Industrial Bio-Test Laboratories. The IBT studies are designated by the letter O. Studies in the EPA data base done by labs other than IBT are designated by the letter X.

The studies are arrayed across six categories of chronic effects. These chronic effects are: oncogenicity, teratogenicity, mutagenicity, reproductive effects, neurotoxicity, and other chronic effects.

Some of the chemicals in this exhibit appear to have no IBT studies because the studies conducted for these chemicals by IBT were all in the acute categories. The chemical names used are those that were listed in the IBT records. There is no designation of the validity or invalidity of the IBT studies presented. Specific information of this nature is in Exhibit B.

Exhibit A also notes any ongoing regulatory activity that will generate chronic data for these chemicals. The types of regulatory activity that cause the generation of data are: the registration standard program, the data call in program, the rebuttable presumption against registration program, and any special action employing the 3c2b provision of the Federal Insecticide, Fungicide, Rodenticide Act. There are approximately 2830 chronic studies indicated in this data base.

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Nemagon	X					XX	
Nemefene	XXX	0	XXXX	00		X 0	
Norea				0		000	Data Call In
Omadine		XXXXXXXX 00000000	X 00	X	XXXXX	XX 000	Discontinued Product Data Call In
Omite-Comite	X	XXXX 0	X	X	0	XX	
Orthene (Acephate)	XXXX 0	XX 00	X 0	XXXX 000	X=12 00000	XXXX 000	
Oxadiazon	X	XXXX	X=16		X	XXX	Data Call In
Paraquat	X	XXXXX	XXXXX	XXXXXXXX	0	XXXX 0	Date Call In
PCNB	XXX	XXXXXX	XXXX	XXXX		X=14	
Penncap E (ethyl parathion)	XX	X	XX	XX	X=37 0	X	

0 = IBT

EXHIBIT B

IBT TRACKING SYSTEM REPORT

IBT TRACKING SYSTEM REPORT

CODE DEFINITIONS

VALIDATE: a review designed to determine if the information in the final report was supported by the raw data from the study.

- I - Invalid. The information in the final report was not supported by the raw data from the study.
- P - Pending. The study is still under validation review.
- S - Supplemental. Portions of the study are valid and can be used independently of the remainder of the study.
- V - Valid. The information in the final report is supported by the raw data from the study.

EVALUATE: a review designed to determine if a study meets Agency guidelines for studies to be used in support of pesticide registration.

- C, CM - Core minimum. The study meets the regulatory data requirements to support pesticide registration.
- S, CS - Core supplemental. The study is useful to supplement other studies.
- I, CI - Core invalid. The study does not meet the regulatory data requirements to support registration.
- P - Pending. The study is still under evaluation review.
- NA - Not applicable. The study was not given an evaluation status if the validation process determined it to be invalid.

REPLACE: the column indicating the replacement status of the study.

- Replaced - Study replaced or in progress
- Discussion - Replacement study under discussion
- Not Req - Study no longer required
- No Resp - No response from registrant
- Neg Resp - Negative response from registrant

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
651-4907	ORTHENE	CHEVRON		REPRODUCTION	DUCK	I	NA	REPLACED
J-2042	ORTHENE	CHEVRON			CATTLE	V	V	NO RESP
J-2493	ORTHENE	CHEVRON			PIG	V	V	NO RESP
J-513	ORTHENE	CHEVRON	NEURO		HEN	I	NA	REPLACED
A-2791	PARAQUAT	CHEVRON	INHALATION	SUBCHRONIC	RAT/PIG/DOG	I	NA	REPLACED
A-3359	PARAQUAT	CHEVRON	DERMAL	SUBACUTE	RABBIT	I	NA	REPLACED
A-3686	PARAQUAT	CHEVRON	DERMAL	SUBACUTE	RABBIT	I	NA	REPLACED
B-1350	PARAQUAT	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-3796	PARAQUAT			SUBACUTE	COW	I	NA	REPLACED
C-1351	PARAQUAT	CHEVRON	ORAL	CHRONIC	DOG	I	NA	REPLACED
D-2723	PARAQUAT	CHEVRON	ORAL	SUBACUTE	COW	I	NA	NEG RESP
D-3030	PARAQUAT	CHEVRON	INHALATION	SUBACUTE	DOG	I	NA	NEG RESP
D-3030	PARAQUAT	CHEVRON	INHALATION	SUBACUTE	GUINEA PIG	I	NA	NEG RESP
D-3030	PARAQUAT	CHEVRON	INHALATION	SUBACUTE	RAT	I	NA	REPLACED
J-131	PARAQUAT	CHEVRON			DUCK	I	NA	NEG RESP
J-131	PARAQUAT	CHEVRON			PHEASANT	I	NA	REPLACED
651-4020	PARAQUAT	CHEVRON	DIETARY		PHEASANT	V	P	REPLACED
651-4381	PARAQUAT	CHEVRON	DIETARY		PHEASANT	V	P	REPLACED
651-5403	PARAQUAT	CHEVRON			HEN	I	NA	NEG RESP
J-131	PARAQUAT	CHEVRON			DUCK	I	NA	NEG RESP
J-131	PARAQUAT	CHEVRON			PHEASANT	I	NA	REPLACED
B-2068	PENNCAP M	PENWALT	ORAL	SUBCHRONIC	RAT	V	CI	NO RESP
J-2040	PENNCAP M	PENWALT	ORAL	SUBCHRONIC	DOG	V		NO RESP
621-4921	PENNCAP M	PENWALT	ORAL	CHRONIC	RAT	I	NA	NO RESP
A-2267	PERFLUIDONE	3M	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
8562-9315	PERFLUIDONE	3M	INHALATION	SUBACUTE	RAT	I	NA	NO RESP
A-6652	PHENMEDIPHAM	NOR AM C	DERMAL	SUBCHRONIC	RABBIT	V		NO RESP
A-7571	PHENMEDIPHAM	NOR AM C		CHOLINESTERASE	RAT	V		NO RESP
B-7149	PHENMEDIPHAM	NOR AM C	ORAL	SUBCHRONIC	RAT	V	NA	REPLACED
C-7150	PHENMEDIPHAM	NOR AM C	ORAL	SUBCHRONIC	DOG	V	NA	REPLACED
M-7657	PHENMEDIPHAM	NOR AM C	INHALATION	SUBCHRONIC	RAT	V		NO RESP
B-8882	PHENTHOATE	MONTEDISON	ORAL	CHRONIC	RAT	I	NA	NEG RESP
C-8884	PHENTHOATE	MONTEDISON	ORAL	CHRONIC	DOG	V	C	NO RESP
601-4413	PHENTHOATE	MONTEDISON	DERMAL	SUBCHRONIC	RABBIT	S	S	NEG RESP
601-4524	PHENTHOATE	MONTEDISON	DERMAL	SUBCHRONIC	RABBIT	I	NA	NEG RESP
622-4624	PHENTHOATE	MONTEDISON		ONCOGENICITY	MOUSE	I	NA	NEG RESP
622-5876	PHENTHOATE	MONTEDISON		MUTAGENICITY	MOUSE	I	NA	NEG RESP
623-3513	PHENTHOATE	MONTEDISON		REPRODUCTION	RAT	S	S	NEG RESP
623-3803	PHENTHOATE	MONTEDISON		REPRODUCTION	RAT	S	I	NEG RESP
632-4157	PHENTHOATE	MONTEDISON		MUTAGENICITY	MOUSE	I	NA	NEG RESP
651-5785	PHENTHOATE	MONTEDISON		TERATOLOGY	RAT	V	P	NEG RESP
651-5875	PHENTHOATE	MONTEDISON		TERATOLOGY	RABBIT	I	NA	NEG RESP
601-3892	PHENTHOATE	MONTEDISON	DERMAL		RABBIT	I	NA	NEG RESP
8580-8635	PHENTHOATE	MONTEDISON	NEURO		HEN	S	S	NEG RESP
C-1292	PHORATE	AKER CYANIMID		CHOLINESTERASE	DOG	I	NA	NO RESP
B-2804	PHOSPHAMIDON	CHEVRON		REPRODUCTION	RAT	I	NA	REPLACED
B-6960	PHOSPHAMIDON	CHEVRON						
	CHOLINESTERASE	RAT	I	NA	NEG RESP			
C-1382	PHOSPHAMIDON	CHEVRON						
ORAL	SUBACUTE	DOG	I	NA	NEG RESP			
C-1444	PHOSPHAMIDON	CHEVRON						
ORAL	CHRONIC	DOG	I	NA	REPLACED			
D-3092	PHOSPHAMIDON	CHEVRON						
	CHOLINESTERASE	RAT	I	NA	NEG RESP			