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Agency

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And Toxic Substances
(7508W)

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EPA

# Pesticide Reregistration Rejection Rate Analysis

## Summary Report

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## Executive Summary

Rejected studies impose large costs on EPA and the pesticide industry and can cause significant delays in meeting reregistration goals. This joint EPA/industry effort is successfully addressing the high rejection rate problem.

- Rejected studies could potential delay as many as 230 more REDs beyond the FY97 statutory deadline than is projected by the Agency's best case scenario which assumes no further study rejections.

- Rejected studies could cost reregistration up to 97,800 additional review hours for scientists to review repeated studies.

- Company-specific rejection rates for reregistration ranged from 20% to 57% in 1991.

- The additional cost to industry to repeat rejected studies in reregistration is estimated at $0.6-$1.2 billion.

- Rejected studies also cause large costs to industry when a new pesticide registration is delayed one or more growing seasons while a rejected study is repeated.

- In 1991, rejection rates for each scientific discipline were: residue chemistry - 12%; toxicology - 7%; environmental fate - 28%; ecological effects - 21%, and occupational and residential exposure - less than 25%.

- As a result of this project residue chemistry's three highest rejection rates have dropped significantly. The processed food study's rejection rate fell from 29% to 16%; the plant metabolism study's rejection rate fell from 27% to 8%; and the crop field trials rejection rate fell from 16% to 12%. Residue chemistry is the only discipline that could be evaluated at this time.

- As a result of this project two companies have reported significant drops in their rejection rates. DowElanco's rejection rate in 1991 was 52%. In 1994 it has fallen to 20%. Rhone Poulenc's rejection rate in 1990 was 45%. In 1994 it has fallen to 13%.

**REJECTION RATE ANALYSIS**

## INTRODUCTION

This report summarizes the process, findings, and recommendations of an evaluation of factors that contributed to rejection of studies submitted to support reregistration.

The purpose of this guideline-by-guideline analysis was to identify those factors that most frequently caused guideline studies required for reregistration to be rejected. This information enabled OPP to (a) provide registrants with information on rejection factors to minimize their recurrence in future studies, (b) reassess the adequacy of its guidance, (c) determine the appropriate regulatory response to a future rejected study, and (d) make any internal changes in process, procedures or criteria deemed appropriate.

The decision to analyze these factors was made after a FIFRA Reregistration recosting analysis, conducted in the Spring of 1991, indicated that rejected studies posed the most significant potential for delays in the production of Reregistration Eligibility Decision documents (REDs). Reregistration eligibility decisions require that reasonable risk assessments be performed for relevant human health and ecological end points for each "substantially complete" data base. A "substantially complete" data base requires that registrants submit studies of acceptable quality. A significant reduction in rejection rates for most disciplines is required for OPP to be able to meet its production schedule for REDS.

This rejection rate analysis has been undertaken by the Special Review and Reregistration Division (SRRD), the Health Effects Division (HED) and the Environmental Fate and Effects Division (EFED) in the Office of Pesticide Programs (OPP) of the Environmental Protection Agency (EPA) in conjunction with industry scientists and the Inter Regional 4 (IR-4) program, which conducts residue chemistry studies to support minor uses.

## PROBLEM STATEMENT

Historically, approximately 30% of the studies submitted to OPP to support the reregistration of pesticide products have been judged unacceptable by Agency scientists.[1] Each rejected study has the potential to delay a RED until the study has been repeated since the appropriate risk assessments may not be able to be conducted until the data base is "substantially complete". In a worse case scenario where rejection rates are formally incorporated into a probabilistic REDs schedule, the Agency estimates that as many as 230 more REDs could be delayed beyond the FY97 statutory deadline than is projected by the Agency's best case scenario which assumed no further studies are rejected. (See Impact on REDs Schedule section). In addition, rejected studies represent a significant increase to the Agency's administrative and science review costs at a time when budgets are being cut. An expected additional 97,800 review hours could be required to review repeated studies.[2]

The cost to the regulated community of rejected studies is also very large. For reregistration, the additional cost to industry to repeat rejected studies is estimated at $0.6 - $1.2 billion.[3] These costs are not borne evenly by registrants. Company-specific rejection rates vary from 20% to 57%.[4] These additional expenditures for repeating rejected studies for existing chemicals, that companies are supporting through reregistration, come out of company research and development budgets that could otherwise be directed towards the development of newer and safer pesticides.

Rejected studies impose potentially large costs to industry and EPA in the registration of <u>new</u> pesticides as well. A rejected study can delay the date when a new registration is granted (while the rejected study is being repeated and then reviewed). Depending on the amount of expected market penetration and the number of missed growing seasons, the loss in sales can be in the tens of millions of dollars per year. Meanwhile, the patent clock, the data compensation clock, and in the case of new uses, the exclusive use clock are all continuing to tick making it more difficult for the company to recover its up front losses over time.

The Agency's concern in registration is three-fold. First, rejected studies create rework to review repeated studies at a time when science review resources are scarce and backlogs of pending actions are high. Secondly, rejected studies cause delays in granting registrations for new and potentially safer pesticides, which could replace riskier ones. Third, delays in granting new registrations can adversely impact growers who need more alternatives to control pests. Reliance on only one pesticide over time to control a pest can accelerate the degree

to which that pest develops resistance to the pesticide. As pest resistance grows, more pesticide use usually results unless another alternative is developed. High rejection rates, then, can frustrate the Agency's goal of use/risk reduction as well.

High rejection rates can also adversely impact the public. First, by delaying reregistration eligibility decisions, the public's lack of confidence in the safety of their food supply and food production system is prolonged. Secondly, by delaying the registration of newer, safer and often lower use-rate pesticides, the public's desire for less pesticide usage and lower pesticide risks is also frustrated.

**IMPACT ON REDS SCHEDULE**

As previously stated, the reregistration recosting analysis conducted in the Spring of 1991 indicated that rejected studies posed the most significant potential for delays in the production of REDs. In their report, Pesticide Reregistration May Not Be Completed Until 2006 (May 1993), GAO recommended that a REDs schedule that formally incorporated the results of the rejection rate analysis be developed. The critical questions that need to be addressed are how many REDs could be delayed by rejected studies and for how long?

By incorporating study-specific rejection rates for each unsatisfied guideline requirement for a chemical, a probabilistic RED schedule can be generated for that chemical. The probability that a chemical will be completed on time or be delayed one, two, three or four years will depend on the number of one, two, three and four-year studies still unsatisfied for that chemical and their corresponding rejection rates.[5] Once probability distributions have been generated for each chemical, the probabilities for a given year can be aggregated across all chemicals to provide the expected number of REDs for that year.

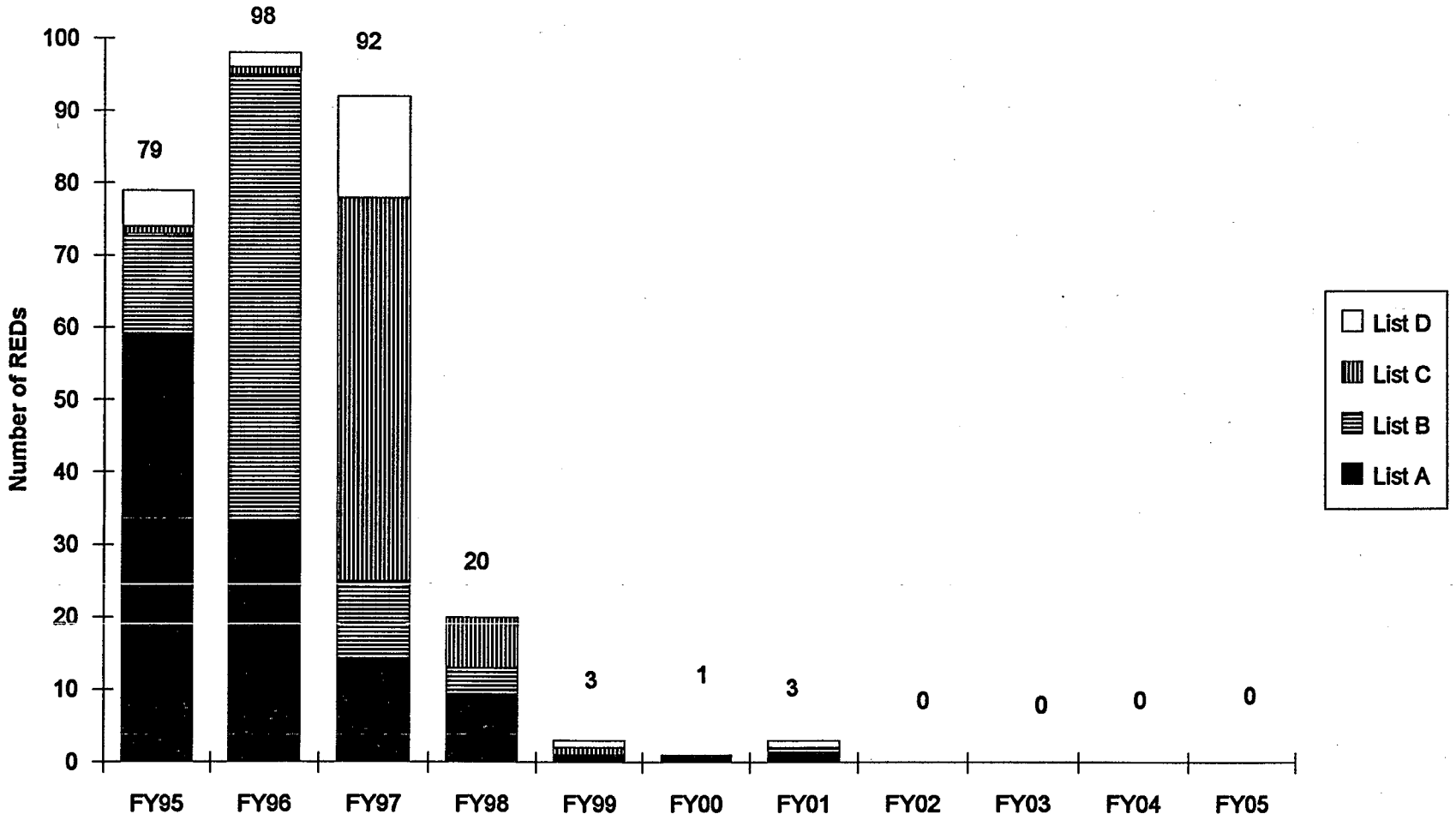
This rejection-rate corrected REDs schedule represents a worst case schedule scenario. First, all rejection rates impact the probability distribution (i.e. amount of delay) for a RED. In reality some rejected studies cause no delay in the RED because the weight of the available evidence allows for a reasonable risk assessment to be performed, and the repeat of the rejected study is considered "confirmatory". Secondly, the full rejection rate is applied to all unsatisfied guidelines including those studies deemed upgradable as well as those studies currently being conducted which are themselves repeat studies. This assumption will result in an overstatement of the probability of delays. Third, it is assumed that rejection rates haven't improved.

The graphs on pages 5 - 15 depict two RED schedule scenarios - - the best case and worst case RED schedules. The most optimistic REDs schedule is titled, the "Earliest Possible REDs Schedule". This schedule is generated by taking the last-study-due-date and adding one year to that date to complete the RED. It assumes that no studies are rejected.

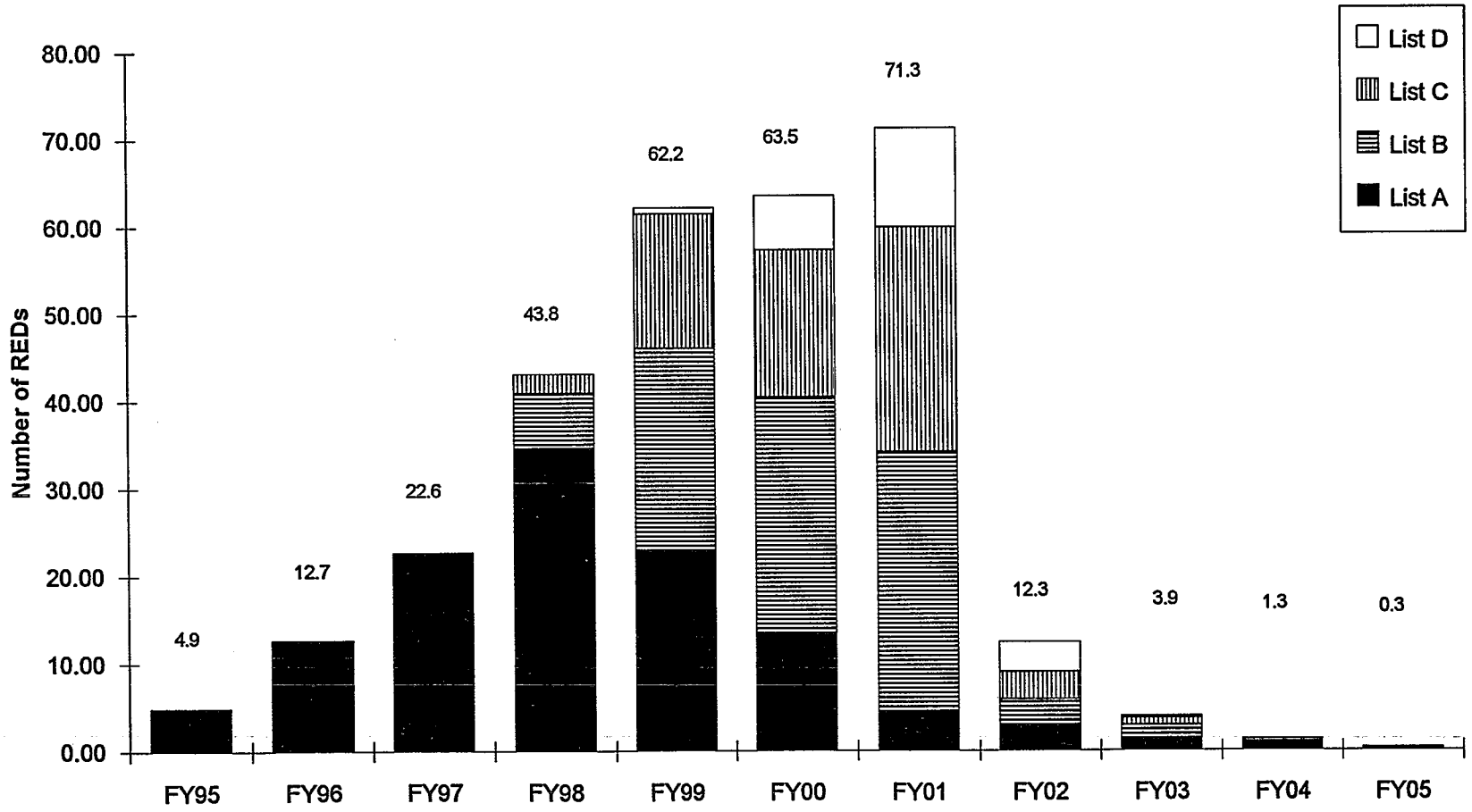
The worst case scenario is the rejection-rate corrected REDs schedule. The worst case scenario projects 230 more REDs could be delayed beyond the FY97 statutory deadline than is projected by the best case scenario. The worst case scenario projects 68 more List A REDs, 87 more List B, and 76 more List C&D REDs could be delayed beyond the FY97 statutory deadline than is projected by the best case scenario.

Actual RED outputs will fall between these two best and worse case scenarios. The more that rejection rates are reduced, the closer actual RED output will come to the best case scenario.

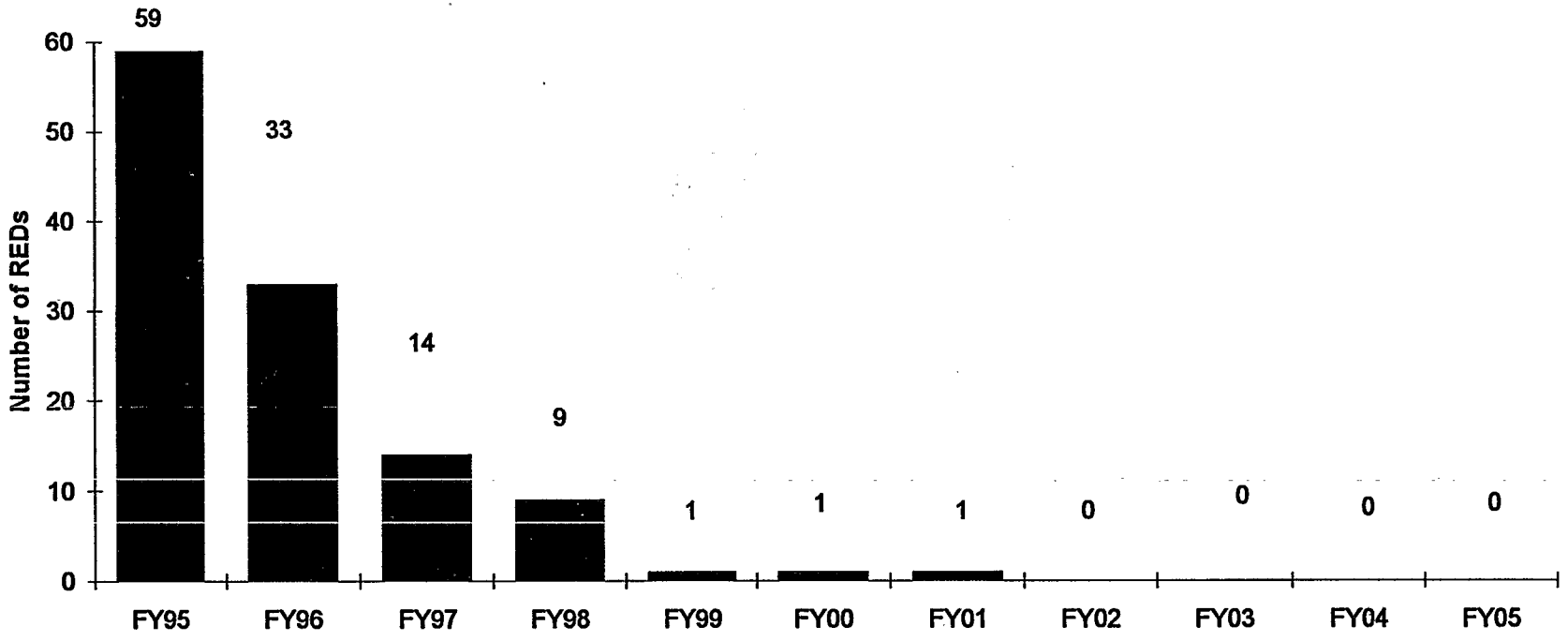
# Earliest Possible RED Schedule
# (All Lists)



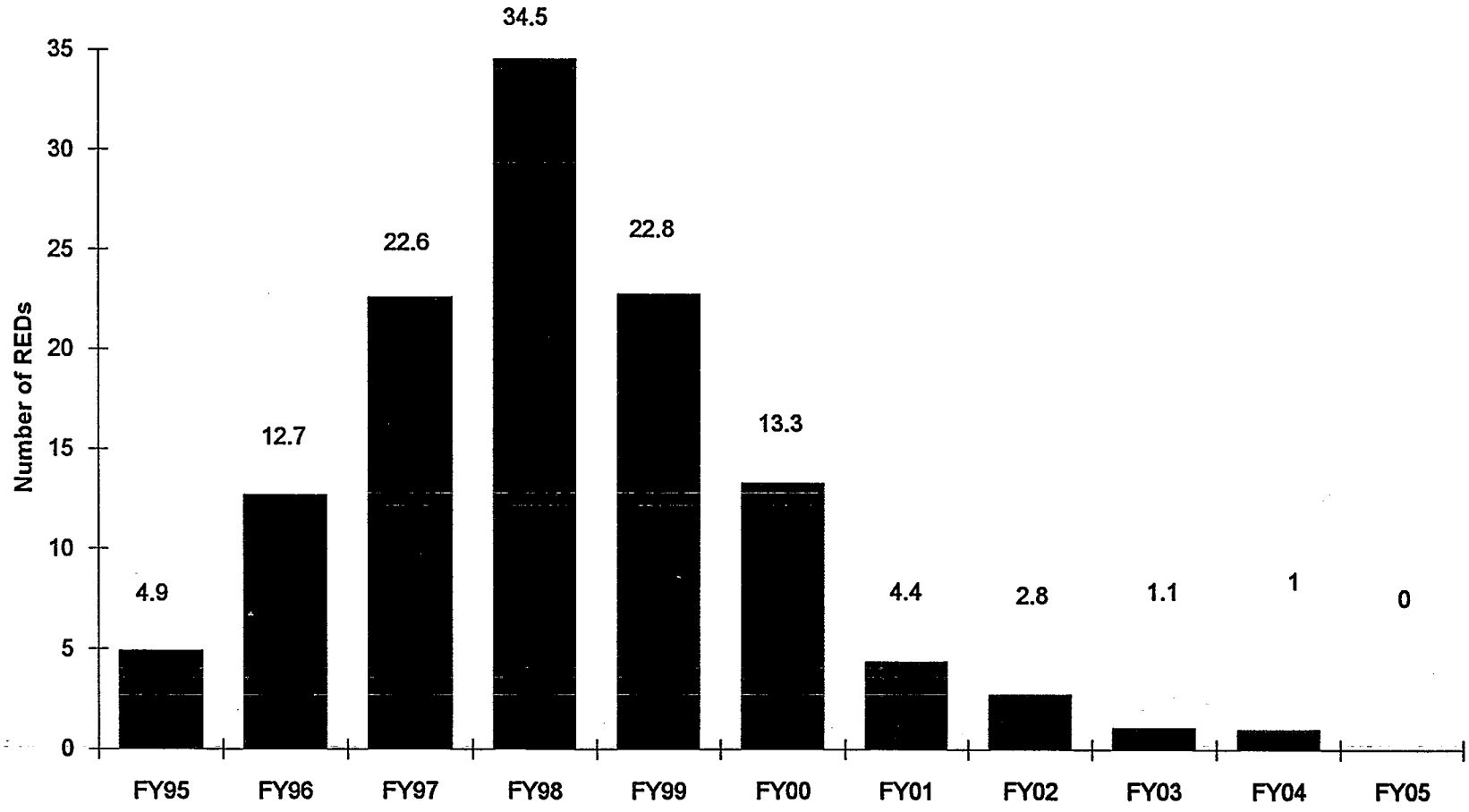
# Worst Case RED Schedule
# (Rejection Rate Correction)
# (All Lists)



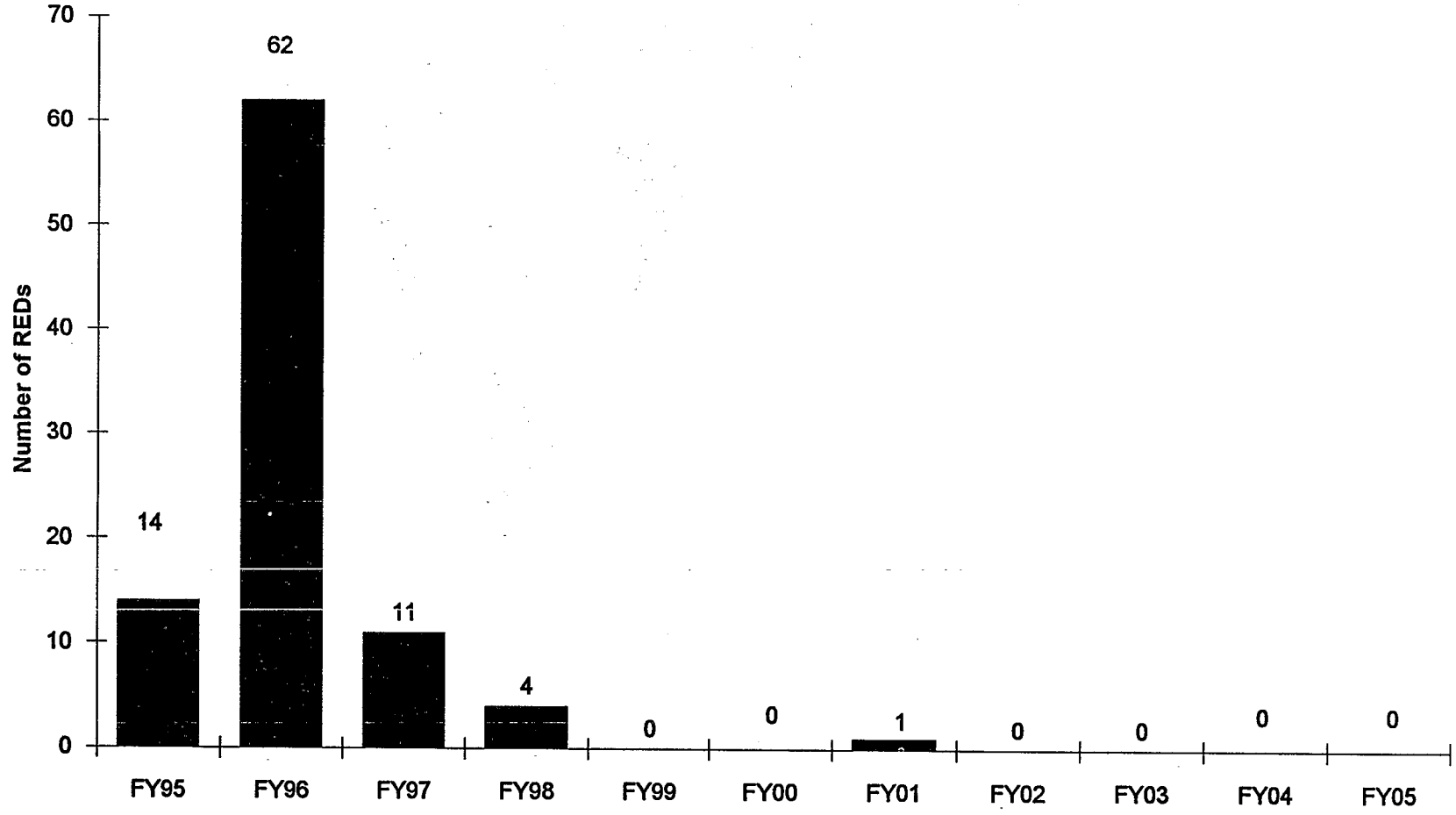
# LIST A
# Earliest Possible RED Schedule
# (LSDD + 1 year)



# LIST A
# Worst Case RED Schedule
# (Rejection Rate Correction)



# LIST B
## Earliest Possible RED Schedule
## (LSDD + 1 Year)

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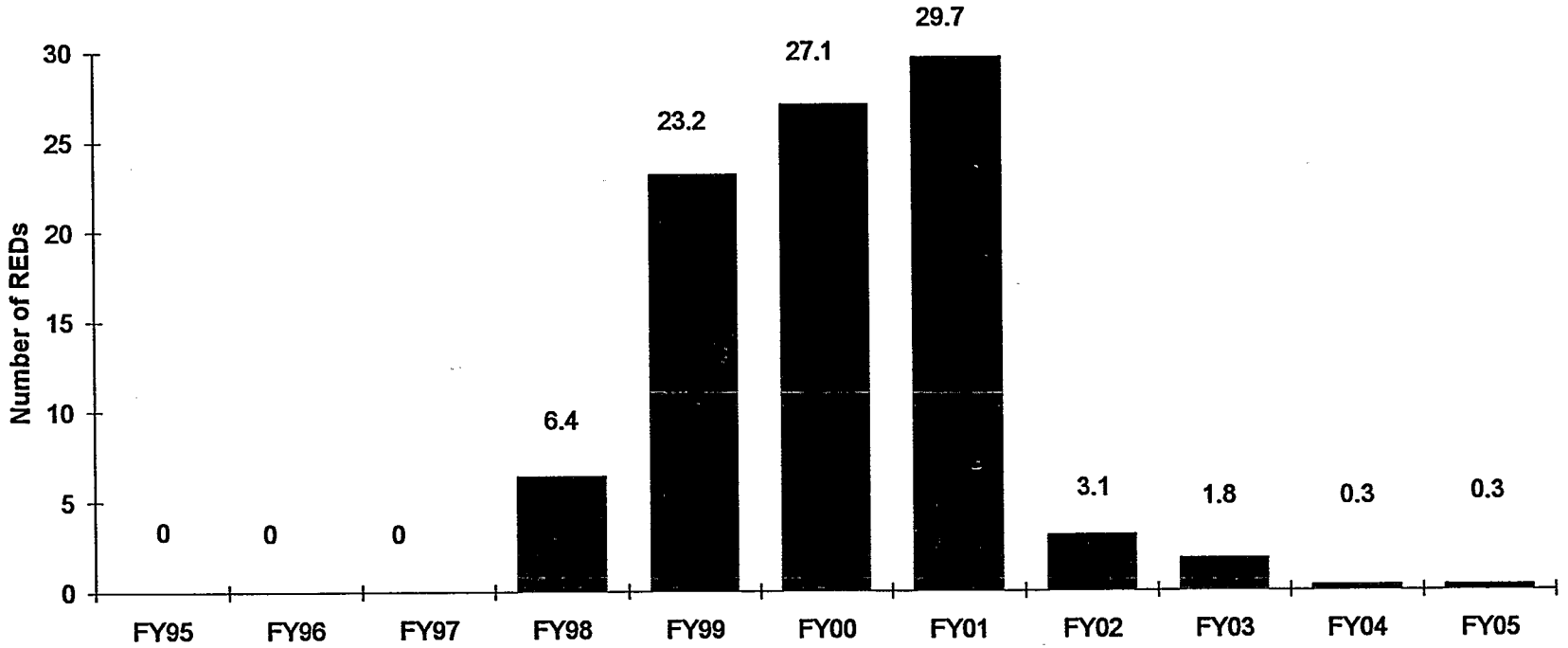
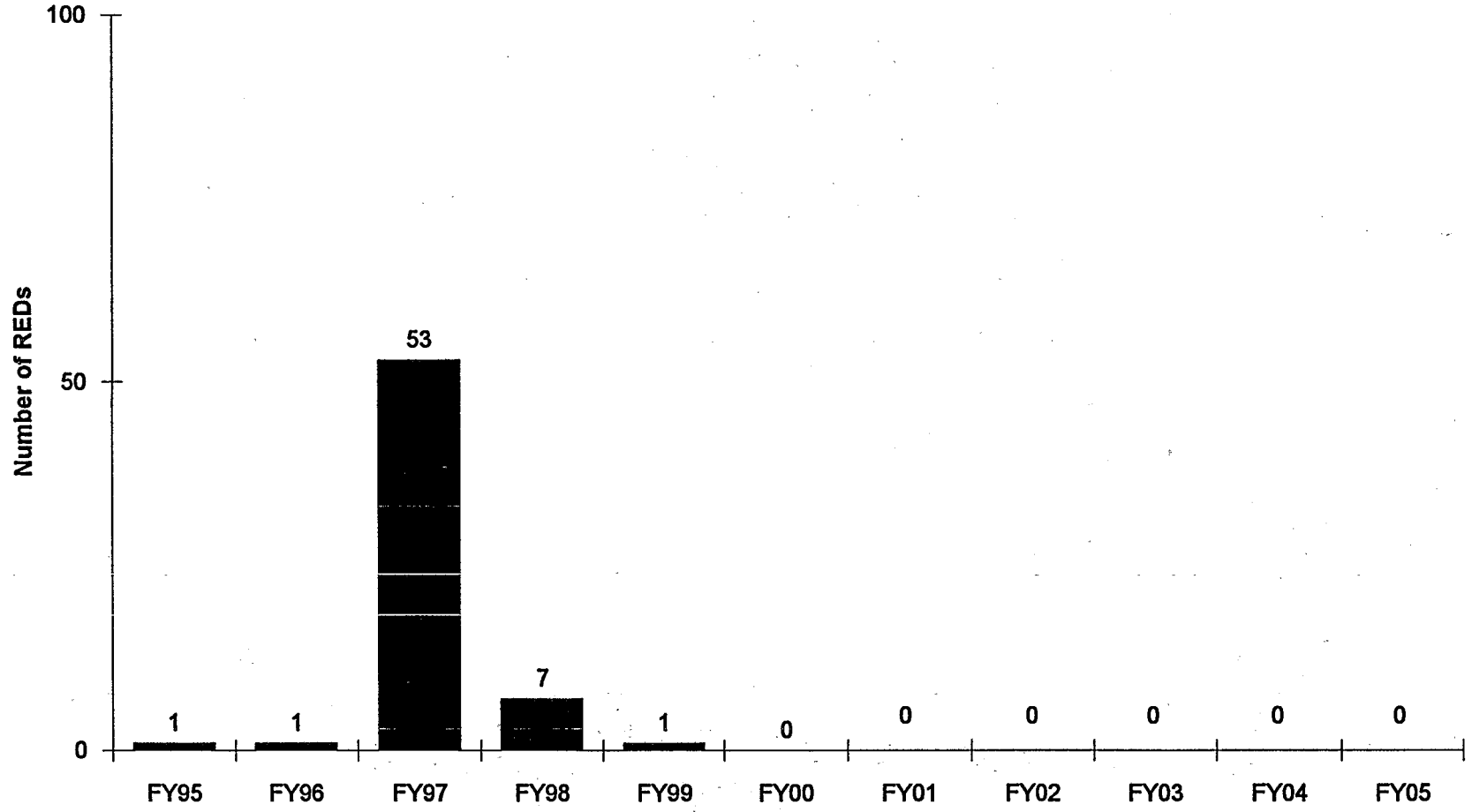
# LIST B
## Worst Case RED Schedule
## (Rejection Rate Correction)



# LIST C
## Earliest Possible RED Schedule
## (LSDD + 1 Year)

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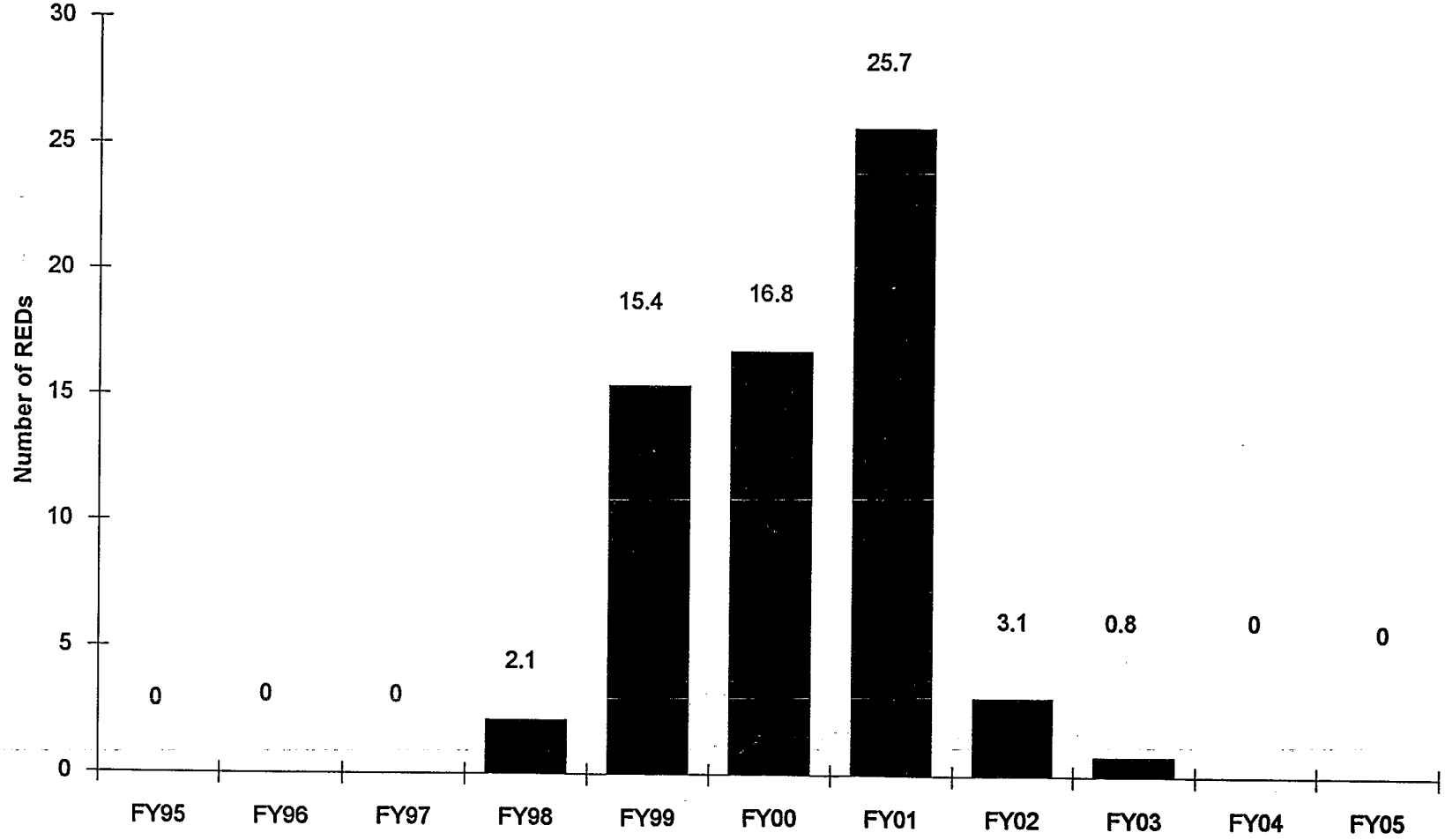
**LIST C**
**Worst Case REDs Schedule**
**(Rejection Rate Correction)**

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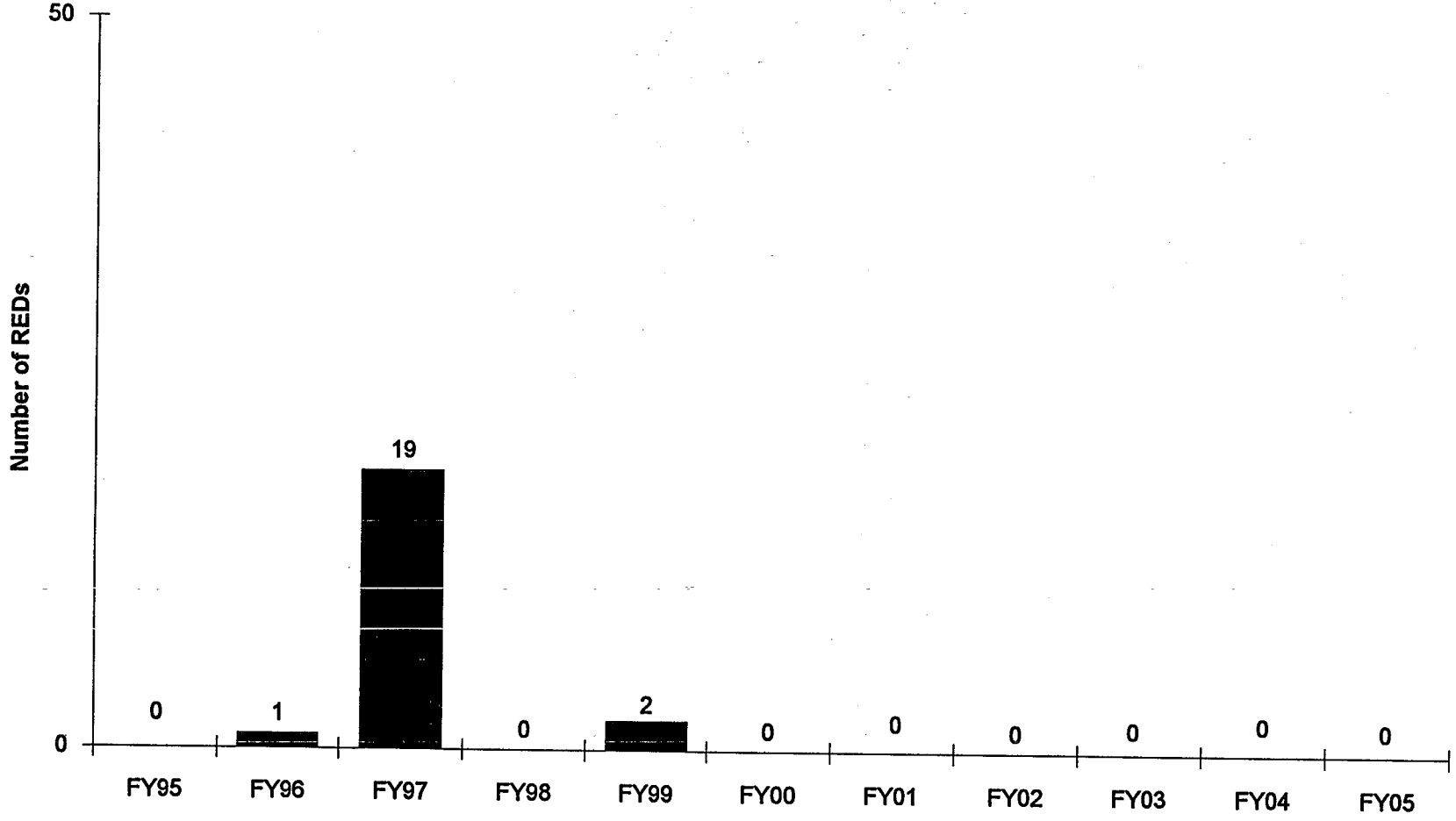
# LIST D
## Earliest Possible RED Schedule
## (LSDD + 1 Year)

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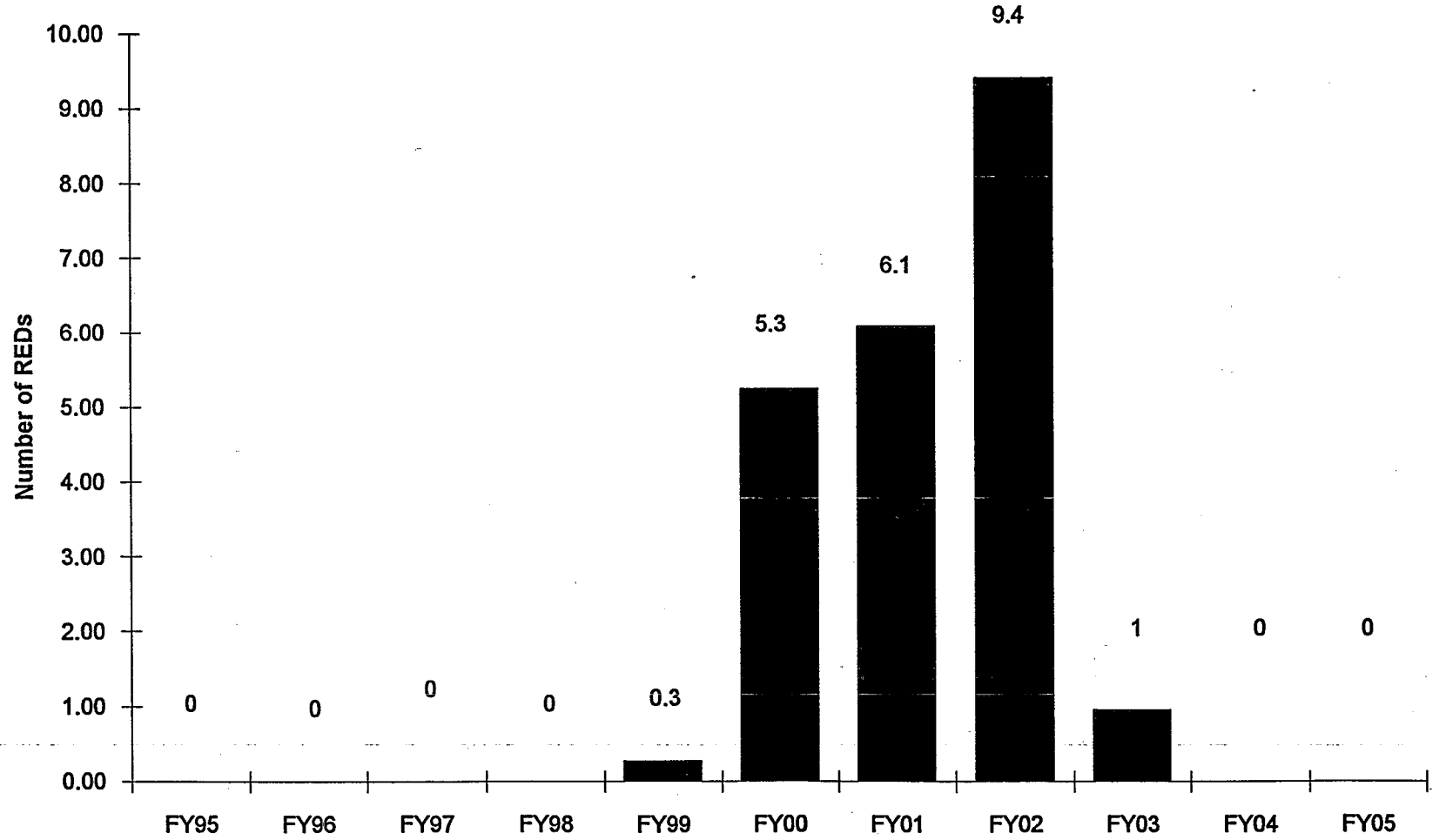
**LIST D**
**Worst Case REDs Schedule**
**(Rejection Rate Correction)**



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**PROCESS**

An initial customer/supplier assessment indicated that OPP is both a customer of industry studies and a supplier to industry of OPP guidance on how to conduct these studies. Conversely, industry is both a supplier to OPP of final studies and a customer of OPP guidance. This interdependent customer/supplier alignment required an assessment of both the rejection factors that most frequently caused studies to be rejected as well as the adequacy of the existing guidance that corresponds to each rejection factor.

First, OPP reviewed the data evaluation records (study reviews by Agency scientists) of rejected studies for each guideline study requirement to identify those factors that most frequently caused each different kind of study to be rejected. Secondly, a workgroup of industry scientists (a) assessed, from a customer's perspective, the adequacy of guidance associated with each rejection factor, (b) explained why rejection factors occurred, and (c) proposed solutions to minimize the reoccurrence of these rejection factors in the future. Third, the industry workgroup submission was reviewed by Agency scientists, and a meeting was held between industry and Agency scientists to discuss each rejection factor, develop the best understanding possible of its underlying causes, and discuss potential solutions. The final step was for Agency scientists to make a final determination of changes required and implement them.

This process was repeated for study requirements in each of the five science disciplines ---- residue chemistry, toxicology, occupational and residential exposure, environmental fate and ecological effects. A separate chapter, that included a description of the discipline, an analysis of rejection rates, identification of rejection factors, discussion of rejection factors by industry scientists and the Agency's final determination of the changes that were required, was published for each science discipline. The residue chemistry chapter was published in July 1992, toxicology in July 1993, environmental fate in September 1993, occupational and residential exposure in September 1993, and ecological effects in December 1994.

**FINDINGS**

The following graphs and lists indicate: (a) the overall rejection rate for each science discipline and how it has changed over time, (b) the rejection rates for each required study in each discipline and how they have changed over time, and (c) the rejection factors that most frequently caused the studies to be rejected. Due to the limited number of studies examined, the rejection rates reported here have not been tested for statistical significance, and therefore caution should be exercised in their interpretation. The purpose is not to develop

an empirically defensible rejection rate value. Rather, the intent is to use rejection rates as the best indicator available of where additional Agency/registrant attention and efforts are warranted to improve the quality of the studies.

(1) Residue Chemistry

Rejection rates for residue chemistry are characterized on the following five graphs. Key implications that might be drawn from these graphs include:

(1) overall rejection rates in residue chemistry appear to have gone down significantly;

(2) the livestock metabolism (171-4B) and crop field trials (171-4K) guidelines have shown substantial declines in their rejection rates;

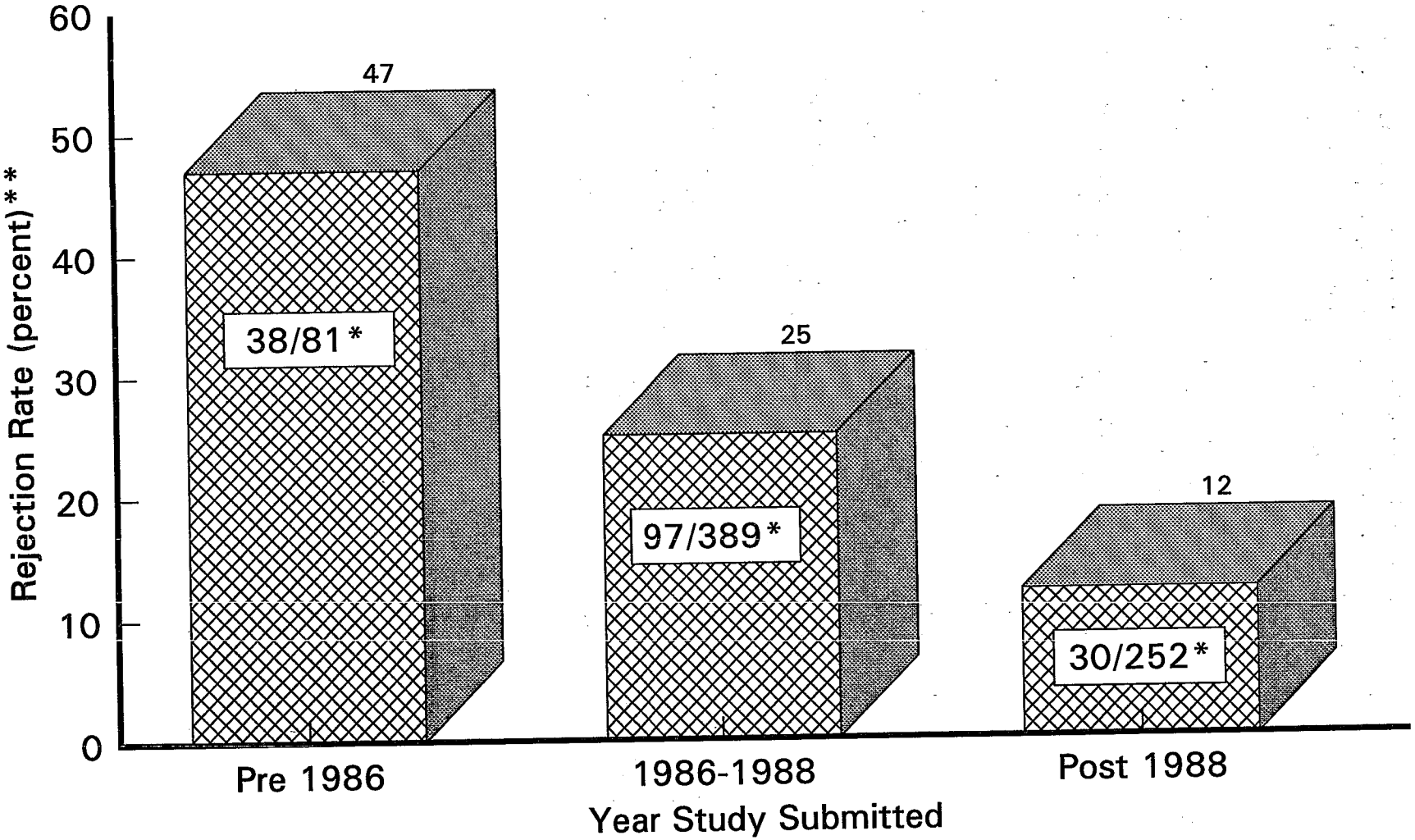
(3) for the plant metabolism (171-4A) and processed food (171-4L) guidelines, the rejection rate trends do not reflect substantial improvement;

(4) processed food (171-4L), plant metabolism (171-4A) and crop field trials (171-4K) still have high rejection rates.

Discussion between Agency and registrant scientists revealed that the tight time frames and limited resources imposed by FIFRA 88 forced industry to start studies before results from other pertinent studies had been reviewed and approved by the Agency. Consequently, rejection factors in the earlier studies cascaded down into the subsequent sequence of studies causing them to be rejected as well.

Figure 1

# List A Rejection Rate For All Residue Chemistry Guideline Requirements



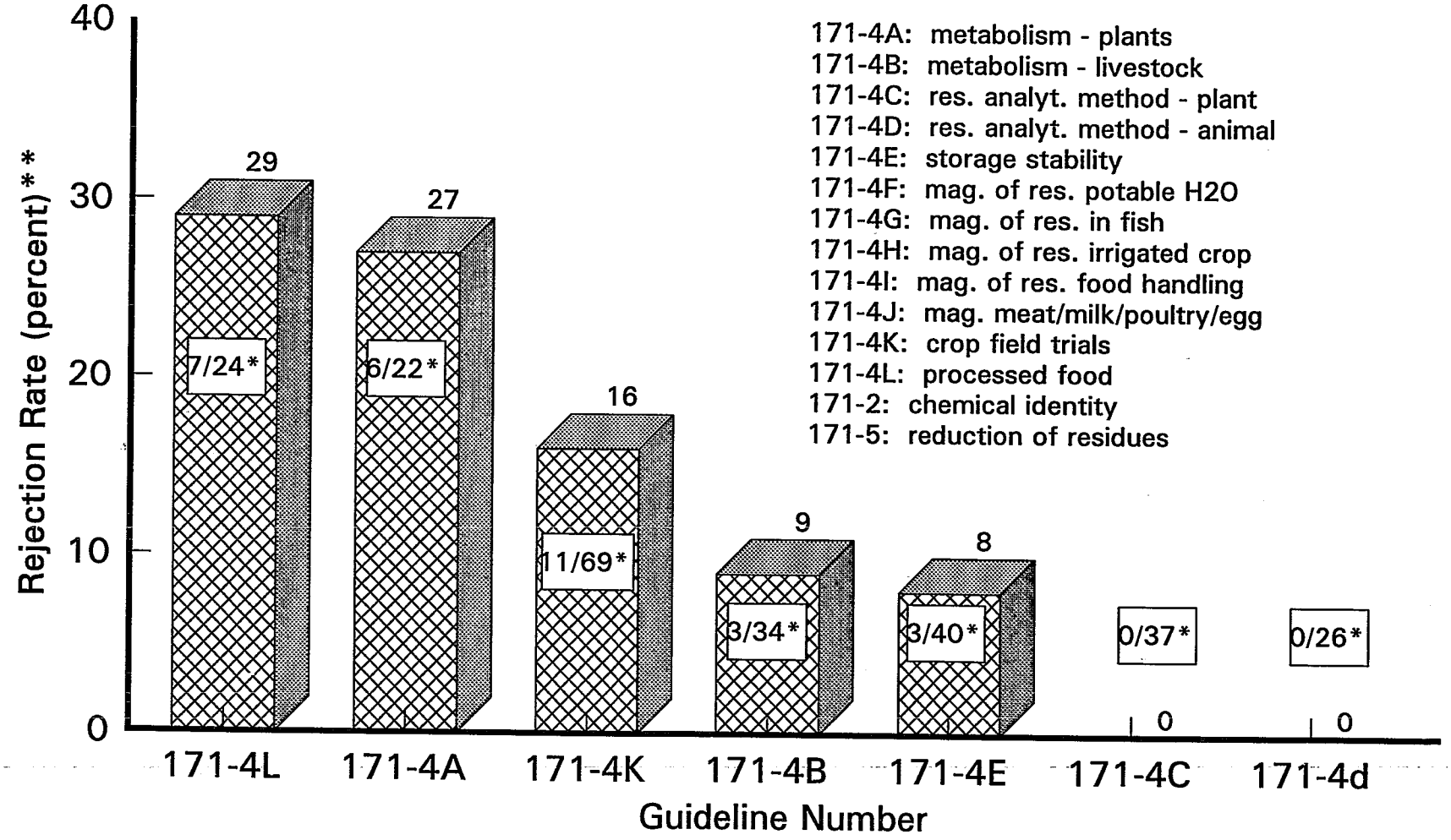

Note: Rejection rates do not include studies submitted prior to Reg. Stnds.

* # rejected studies/# studies reviewed

** Of the total number of studies reviewed under that guideline, the percentage of studies that were rejected

Figure 2

# List A - Current (Post 1988) Rejection Rates by Residue Chemistry Guideline



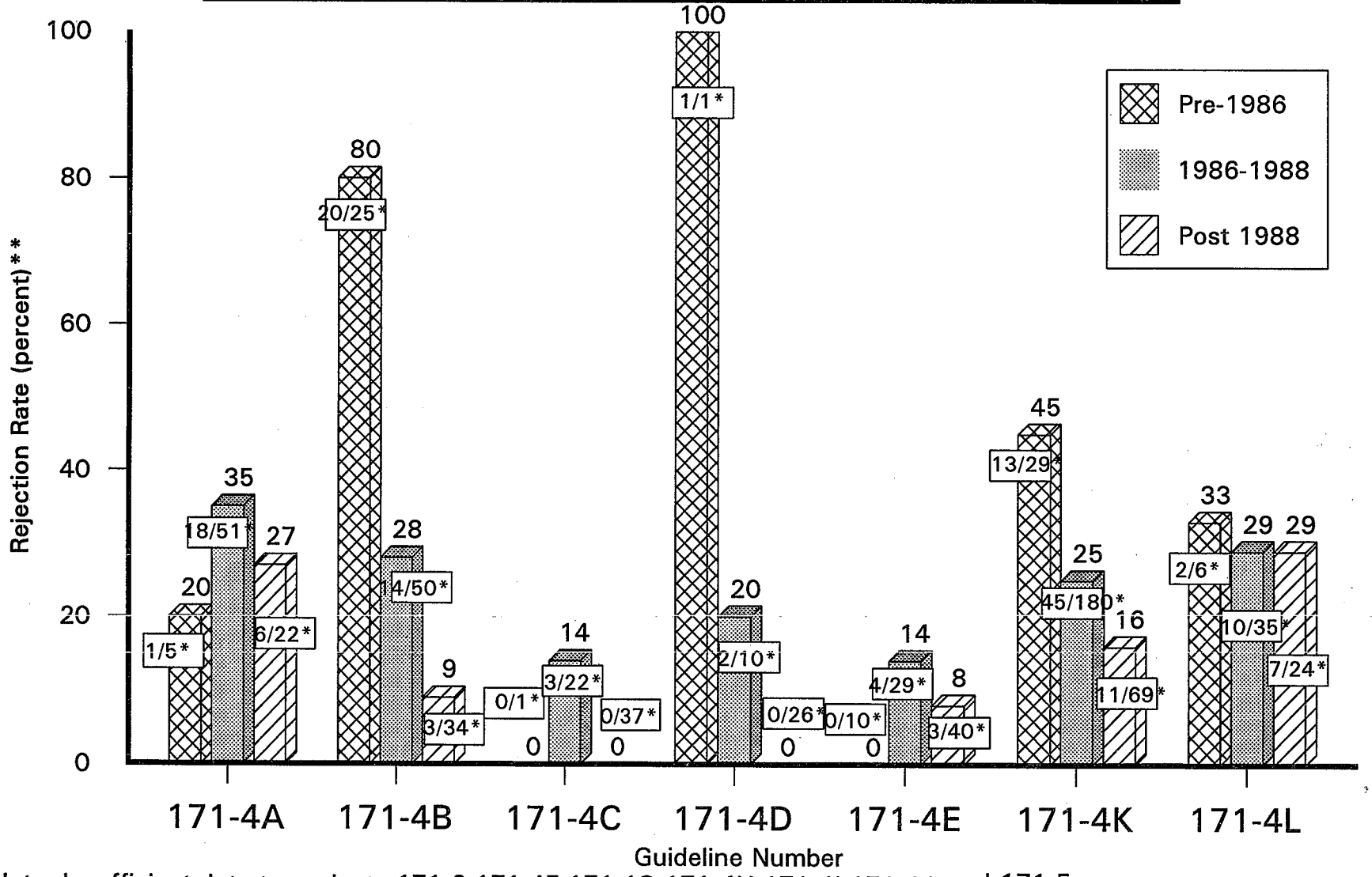

* # rejected studies/# studies reviewed

** Of the total number of studies reviewed under that guideline, the percentage of studies that were rejected

Note: Insufficient data to evaluate 171-2,171-4F,171-4G,171-4H,171-4I,171-4J, and 171-5.

Figure 3

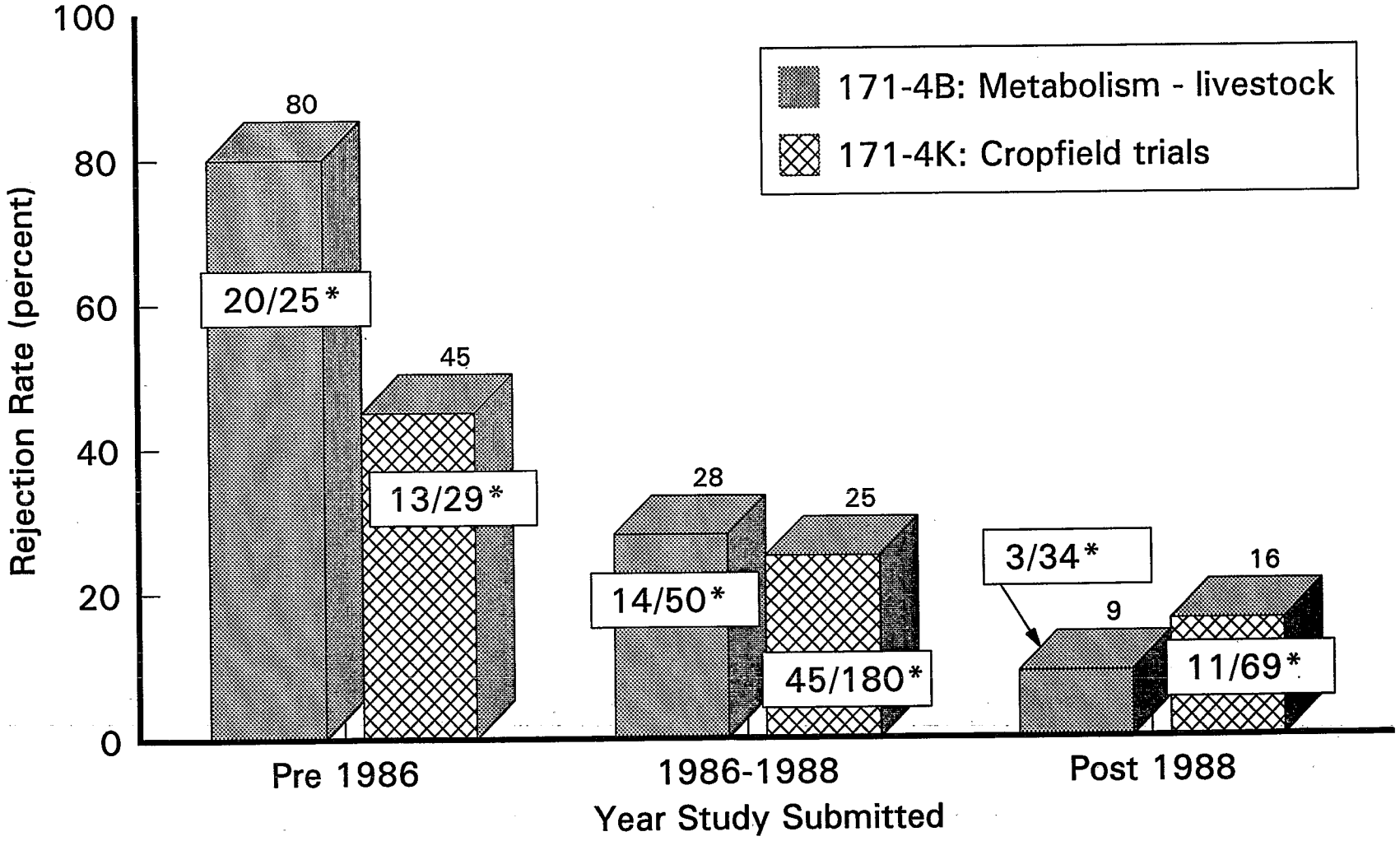
# List A - Residue Chemistry Rejection Rate By Guideline Since Before 1986




Note: Insufficient data to evaluate 171-2,171-4F,171-4G,171-4H,171-4I,171-4J, and 171-5.
Rejection rates do not include studies submitted prior to Reg. Stnds. * # rejected studies/# studies reviewed

Figure 4

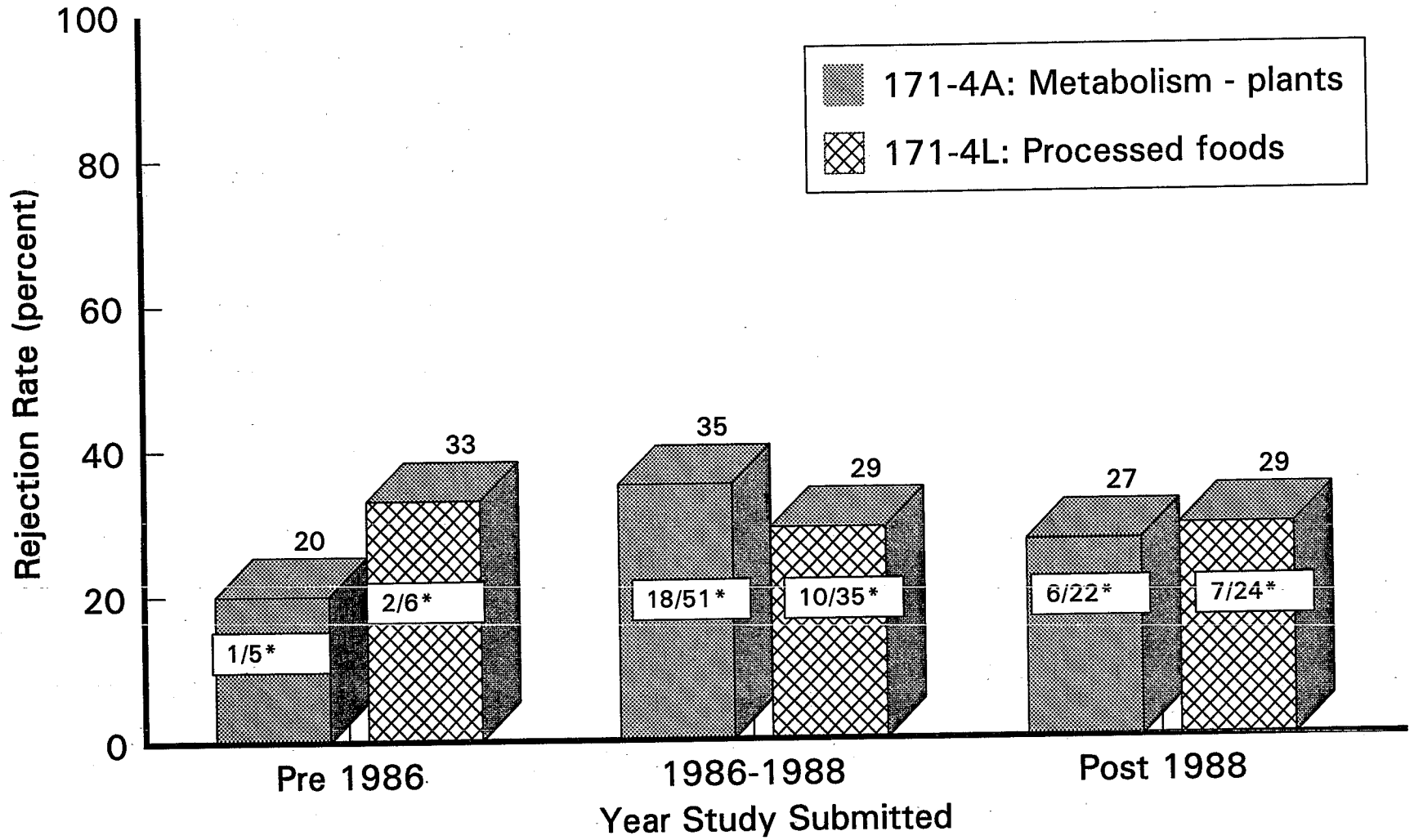
# List A Residue Chemistry Guidelines With Lower Rejection Rates Over Time




* # rejected studies/# studies reviewed

Figure 5

# List A Residue Chemistry Guidelines With Constant Rejection Rates




* # rejected studies/# studies reviewed

## SUMMARY TABLE OF REJECTION FACTORS - RESIDUE CHEMISTRY

| GUIDELINE | REJECTION FACTOR |
|---|---|
| **PLANT METABOLISM STUDIES:** 171-4A | -No characterization of residues<br>-Partial characterization of residues<br>-Characterization conducted on immature crop parts/cell cultures<br>-Plants treated with wrong material such as an isomer of the pesticide or pesticide radiolabeled in a potentially labile site<br>-Application of pesticide at less than maximum registered rates<br>-Need for confirmation of residue identities by second technique |
| **LIVESTOCK METABOLISM STUDIES:** 171-4B | -No characterization of residues<br>-Dosing with a mixture of compounds<br>-Partial characterization of residues<br>-Animals dosed with wrong material such as an isomer of the pesticide or pesticide radiolabeled in a potentially labile site<br>-Need for confirmation of residue identities by second technique |
| **ANALYTICAL METHODS:** 171-4C,D | -Method inadequately validated |
| **STORAGE STABILITY:** 171-4E | -Samples not fortified with all components of the total toxic residue<br>-Fortification with a mixture<br>-Use of an Analytical method which gives low and variable recoveries<br>-Insufficient information regarding dates, storage conditions, and descriptions of analytical methods<br>-Failure to include a sufficient range of commodities |
| **CROP RESIDUE STUDIES:** 171-4K | -Method inadequately validated or described<br>-Insufficient geographical representation<br>-No data for aerial/sprinkler application on label<br>-Relevant formulation not tested<br>-Registered use/minimum PHI not reflected<br>-Inadequate storage stability data<br>-Application number/rate too low<br>-Untreated RAC contaminated<br>-Summary data presented, not supported by raw data<br>-No data on relevant metabolites<br>-No data on relevant commodity |
| **FOOD PROCESSING STUDIES:** 171-4L | -No data on relevant commodity<br>-Method - Inadequate description/validation data<br>-Exaggerated application rate needed<br>-No data on storage conditions/stability<br>-Application rate less than maximum<br>-Relevant metabolite not analyzed |

(2) Toxicology

Rejection rates for toxicology are characterized on the following seven graphs. Key implications that might be drawn from these graphs include:

(1) Overall rejection rates in toxicology are low and have remained relatively constant.

(2) A substantial number of toxicology studies have been rated supplementary (i.e., upgradable), and the supplementary rate appears to be rising.

(3) The CORT studies have shown substantial declines in their rejection rates.

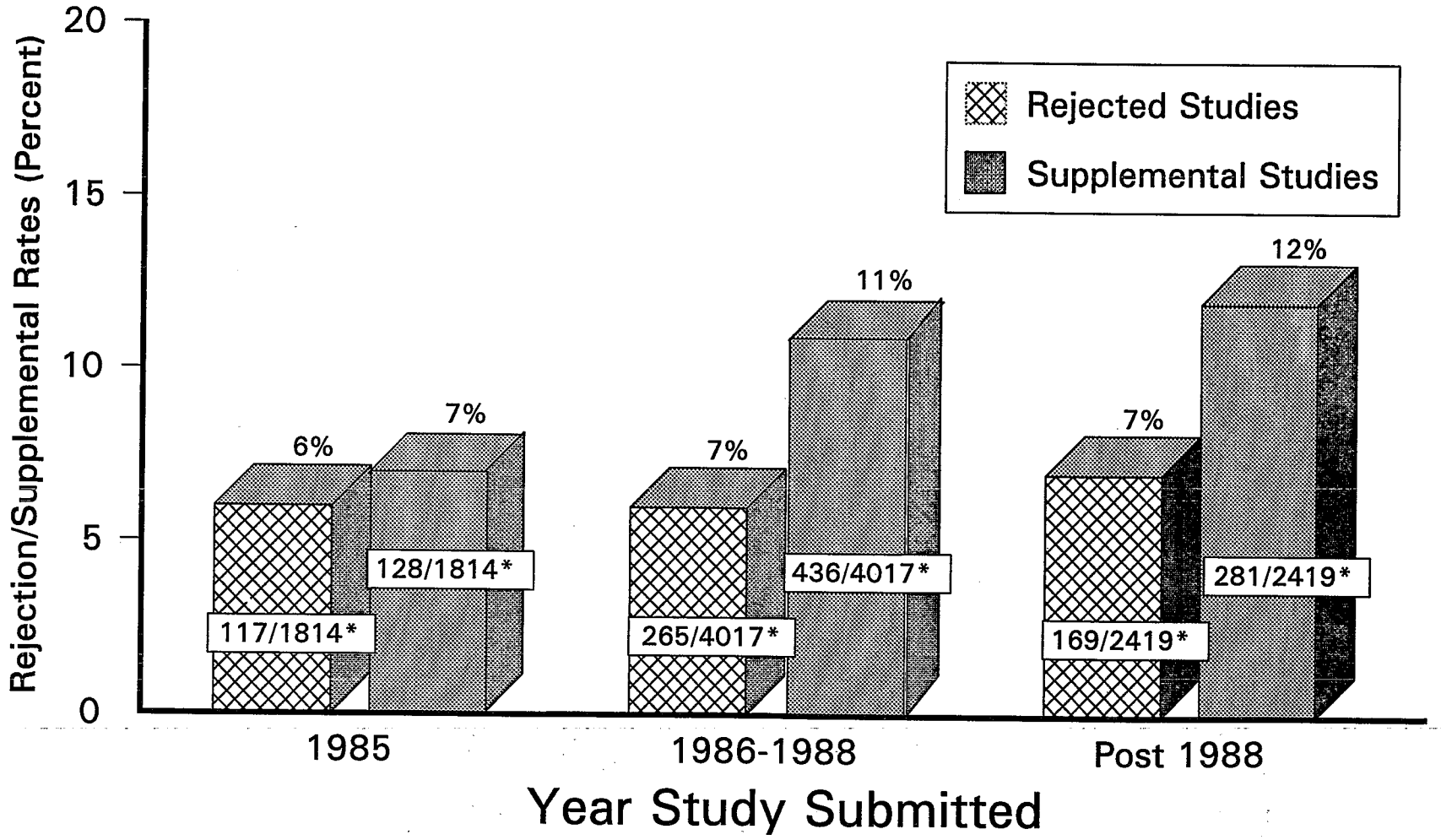
(4) The Mutagenicity studies and the General Metabolism study have also shown decreasing rejection rates.

(5) Dermal Penetration, Subchronic 90-day Feeding -rat, Acute Dermal Sensitization studies have all shown substantial increases in their rejection rates over time.

The Agency also reviewed the amount of time that had elapsed in attempting to upgrade supplementary studies and found, in some cases, that it took five, six, or even seven years, which is significantly more time than is required to repeat the study. The long elapsed times of four years or more occurred for studies submitted between 1985 and 1988 before the initiation of FIFRA 88. While the long lapse times may accurately reflect past Agency/registrant performance, there is good reason to believe that the results do not accurately reflect current performance. First, FIFRA 88 desk top computers have been provided to all chemical review managers (CRMs) and product managers (PMs) and data tracking systems have been developed and implemented. Prior to FIFRA 88, only a limited access main-frame tracking system was available. Thus, the Agency's capability to track the timeliness of responses and reviews has been greatly enhanced. Second, prior practice did not require imposing time limits on registrant response for supplementary data. In reregistration, all supplementary data requests have a time limit imposed. Third, in reregistration all supplementary-data-request correspondence is sent as certified mail to ensure that the registrant receives it.

Figure 1

# Rejection and Supplemental Rates For All Toxicology Guideline Requirements

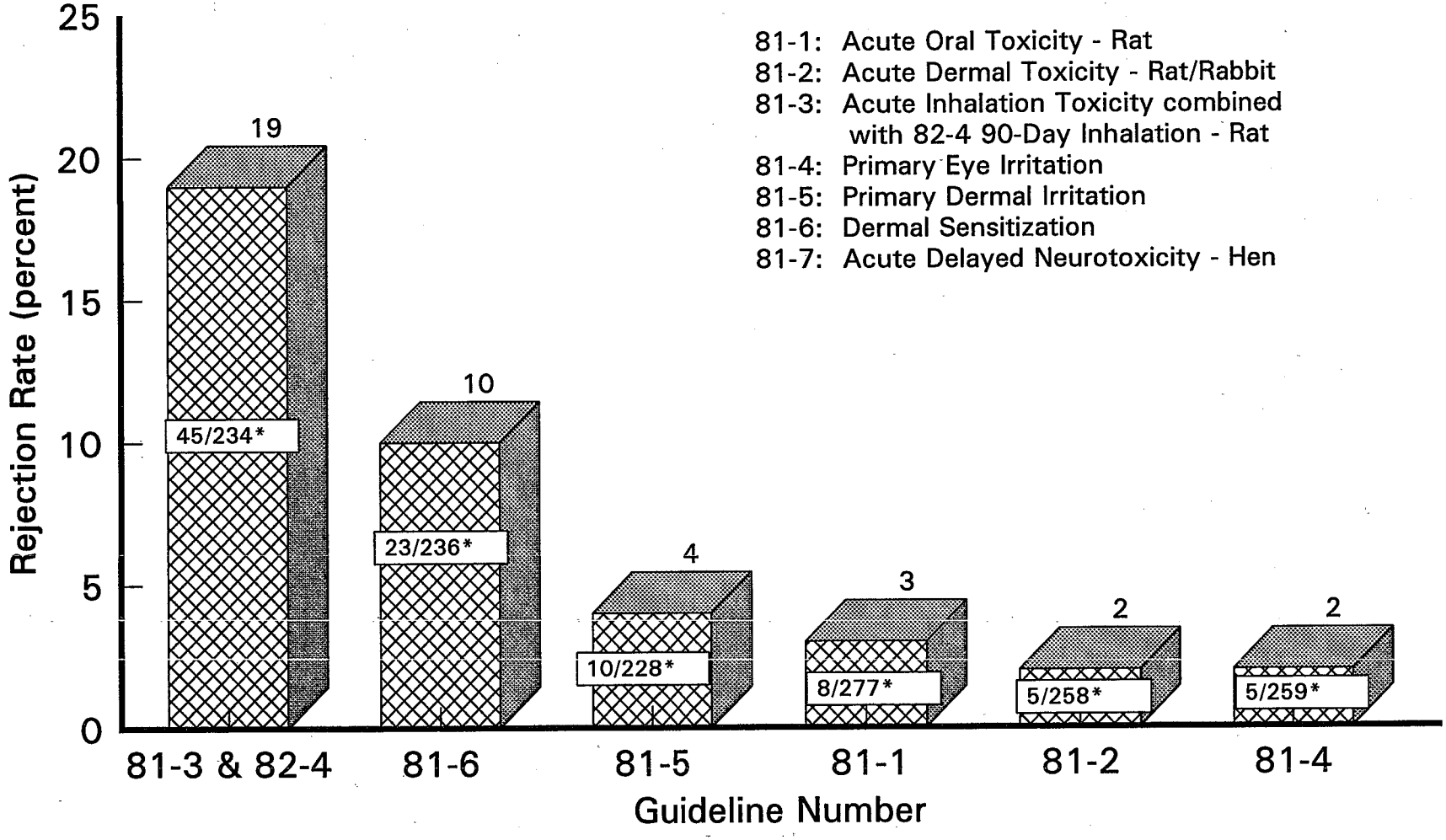



* # rejected studies/# studies reviewed

Note: Studies reviewed include studies from List A,B,C, & D as well as from chemicals registered after 1984.

Figure 2

# List A - Current (Post 1988) Rejection Rates by Guideline - Acute Toxicity

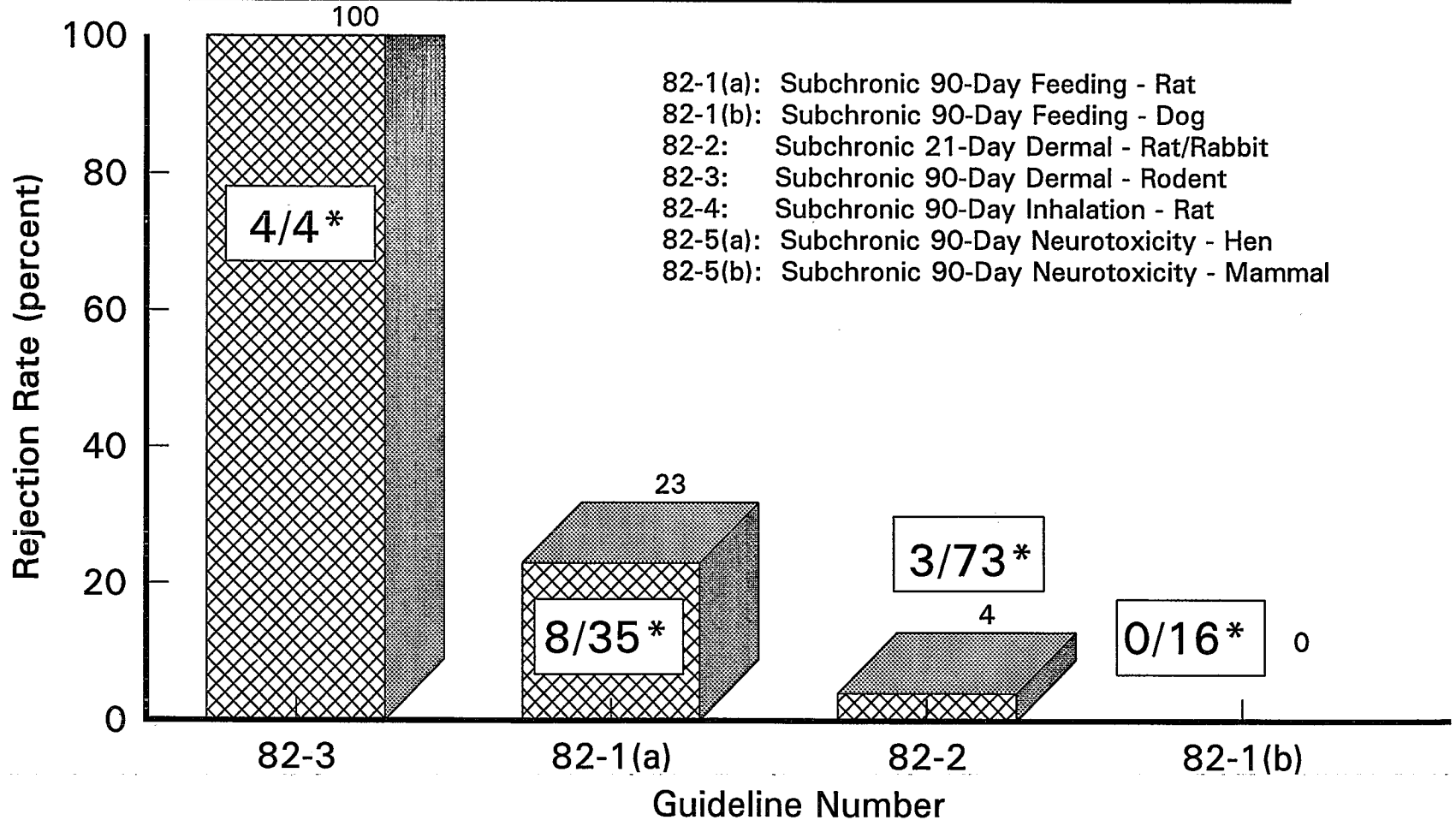



* # rejected studies/# studies reviewed

Note: Insufficient data to evaluate 81-7.

Figure 3

# List A - Current (Post 1988) Rejection Rates by Guideline - Subchronic Toxicity

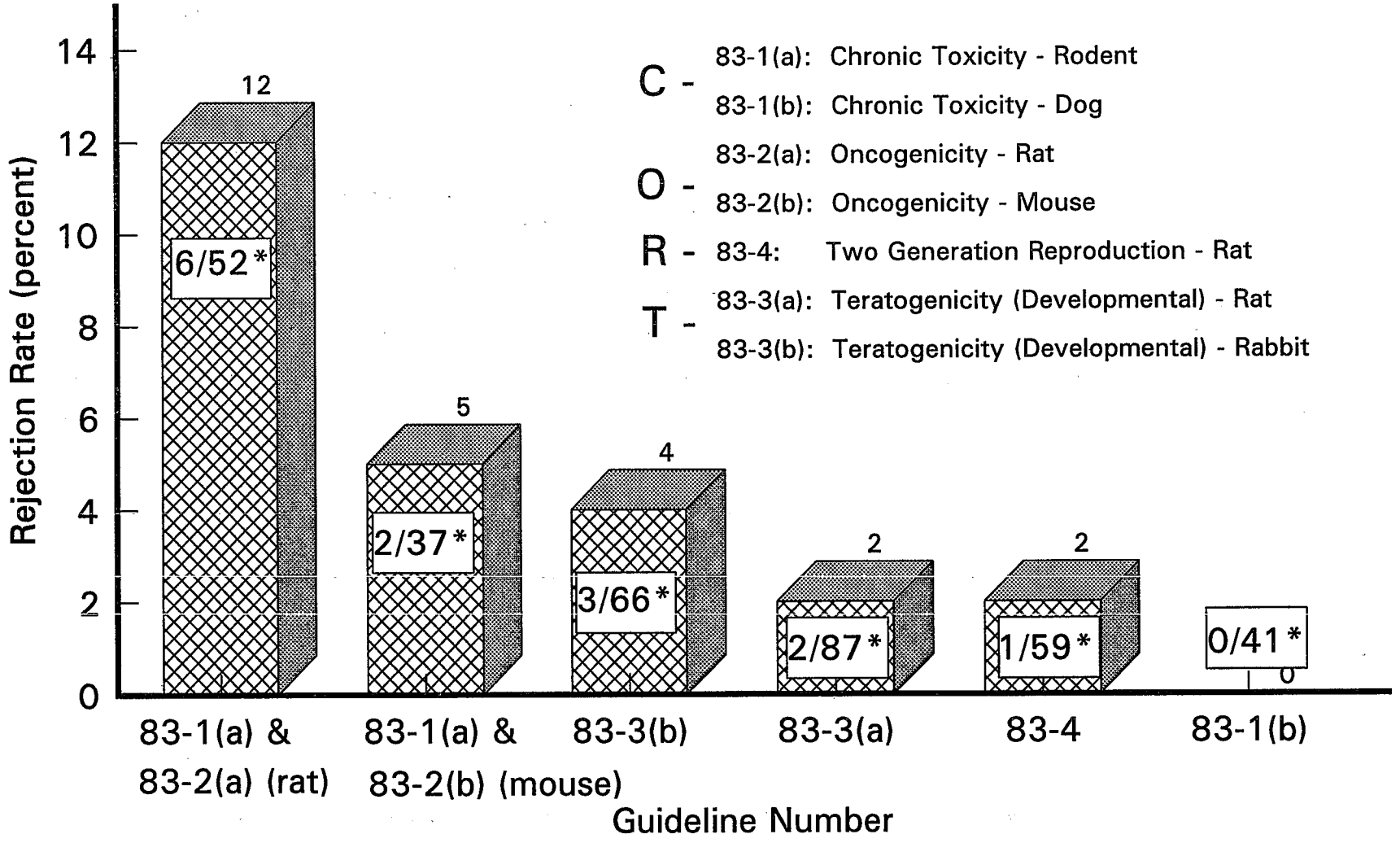



* # rejected studies/# studies reviewed

Note: Insufficient data to evaluate 82-5(a) and 82-5(b); 82-4 combined with 81-3 in Figure 2.

Figure 4

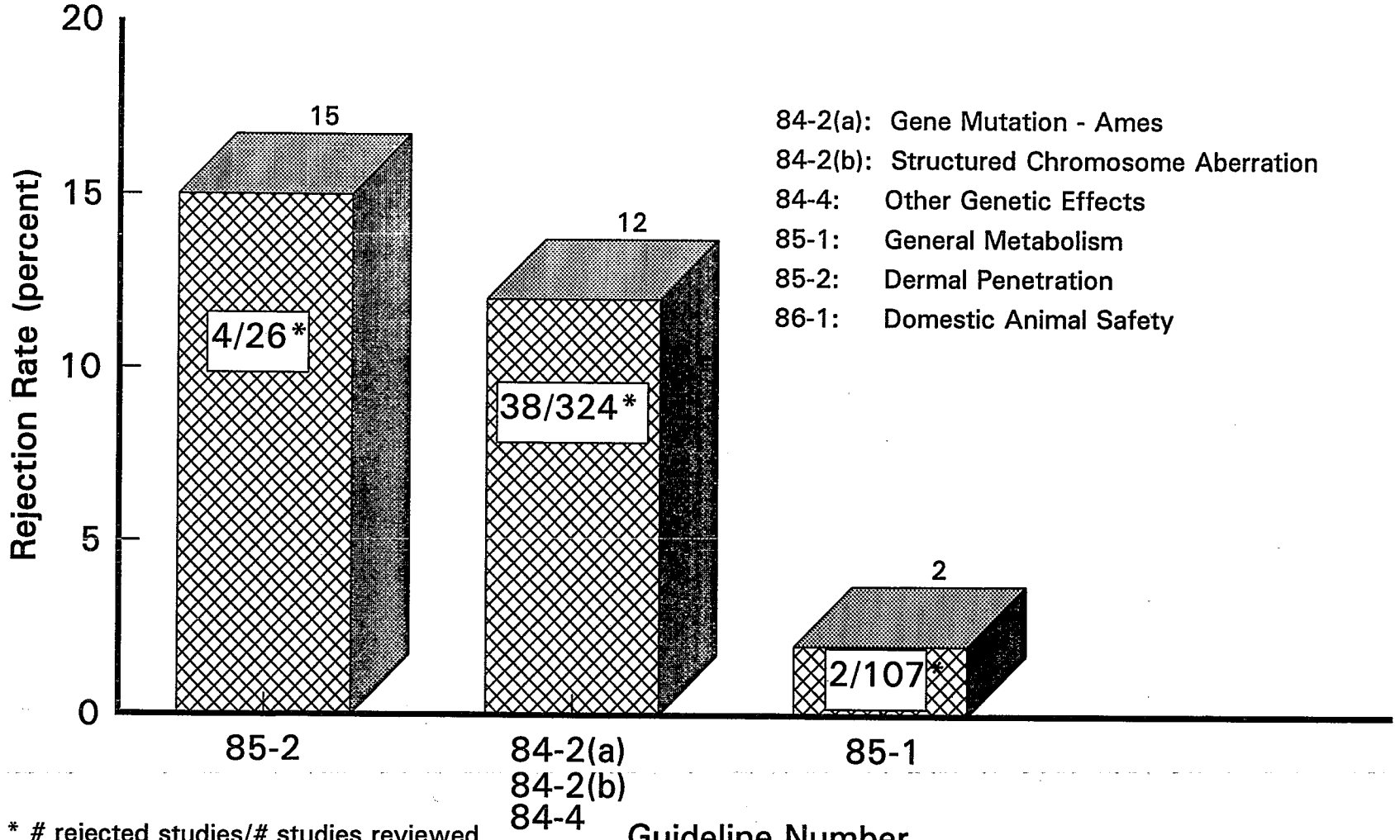
# List A - Current (Post 1988) Rejection Rates by Guideline - CORT Studies




* # rejected studies/# studies reviewed

Figure 5

# List A - Current (Post 1988) Rejection Rates by Guideline - Other Toxicology Studies

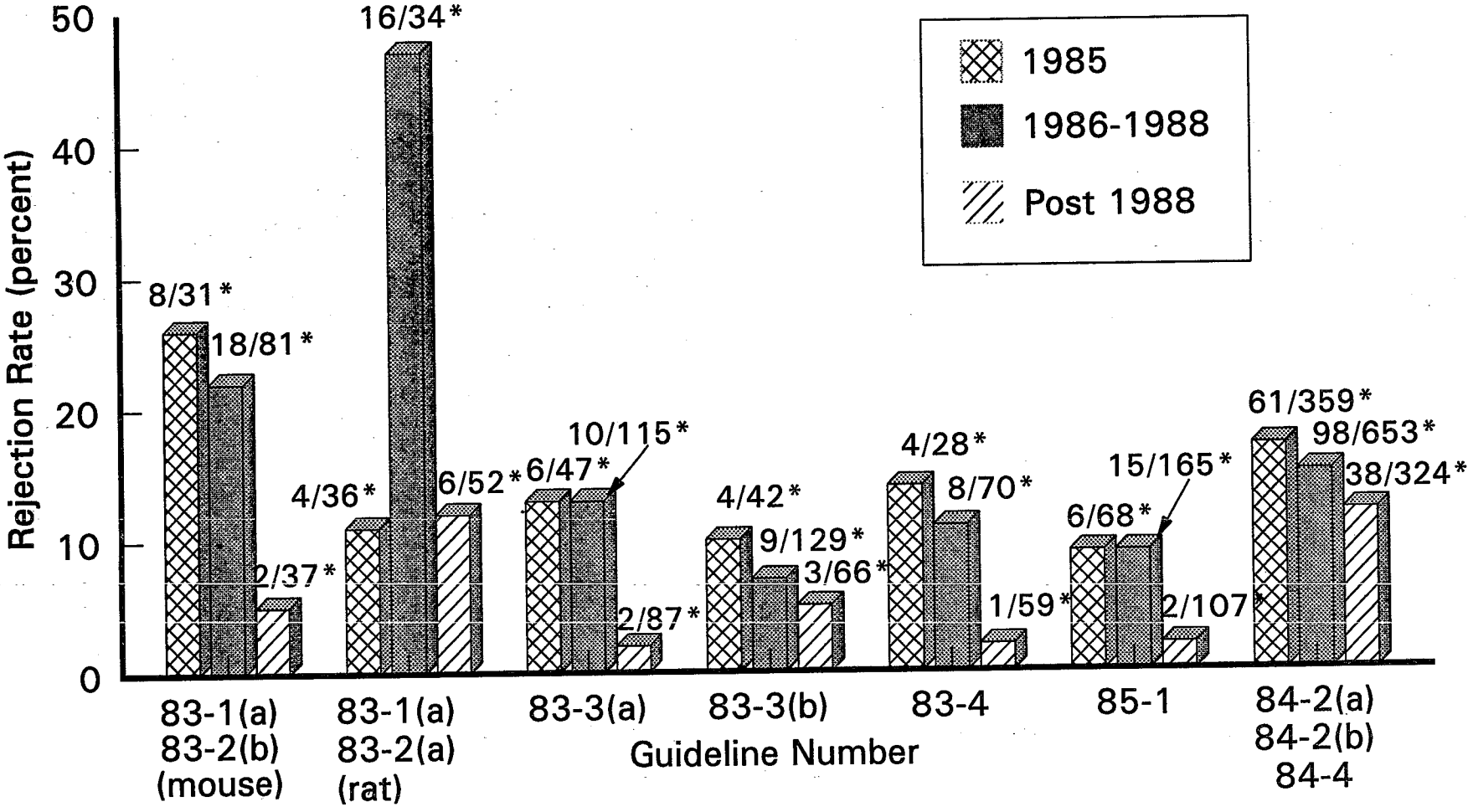



* # rejected studies/# studies reviewed

Note: Insufficient data to evaluate 86-1.

Figure 6

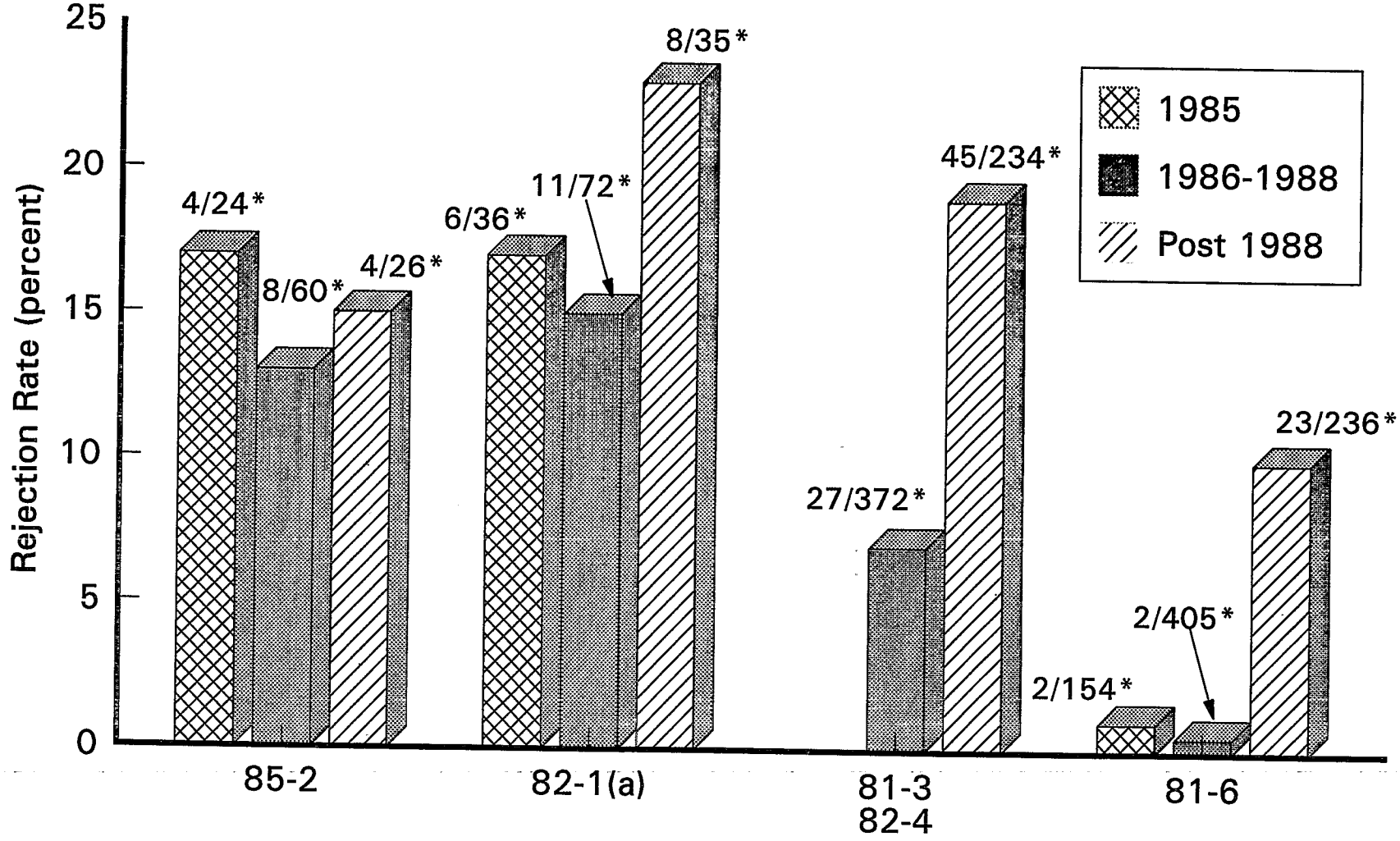
# Toxicology Guidelines with Lower Rejection Rates Over Time




* # rejected studies/# studies reviewed

Figure 7

# Toxicology Guidelines with Increasing Rejection Rates Over Time




* # rejected studies/# studies reviewed

## SUMMARY TABLE OF REJECTION FACTORS - TOXICOLOGY

| GUIDELINE | REJECTION FACTOR |
|---|---|
| **ACUTE ORAL TOXICITY**<br>81-1 | -Lack of characterization of the test substance<br>-Inadequate dose levels to calculate LD50 |
| **ACUTE DERMAL TOXICITY**<br>81-2 | -Lack of characterization of the test substance<br>-Inadequate percentage of body surface area exposed<br>-No quality assurance statement<br>-Improper number of animals tested per dose group<br>-Only one sex tested<br>-Omitted source, age, weight, or strain of test animal |
| **ACUTE AND 90-DAY INHALATION**<br>81-3 and 82-4 | -Less than 25% of particles were < 1 $\mu$m<br>-Three exposure concentrations were not used; LC50 could not be calculated; highest concentration did not produce toxicity<br>-Inadequate reporting of exposure methodology<br>-Protocol errors<br>-Lack of characterization of the test substance<br>-Test substance preparation<br>-Chamber concentration not measured |
| **PRIMARY EYE IRRITATION**<br>81-4 | -Lack of characterization of the test substance |
| **PRIMARY DERMAL IRRITATION**<br>81-5 | -Lack of characterization of the test substance<br>-No quality assurance statement and/or no Good Laboratory Practice (GLP) statement<br>-Improper test substance application/preparation<br>-Omitted source, age, weight, or strain of test animal<br>-Missing individual/summary animal data |
| **DERMAL SENSITIZATION**<br>81-6 | -Control problems<br>-Dosing level problems<br>-Lack of characterization of the test substance<br>-Unacceptable protocol or other protocol problems<br>-Individual animal scores or data missing<br>-Scoring method or other scoring problem<br>-Reporting deficiencies or no quality assurance statement |

| | |
|---|---|
| **90-DAY FEEDING - RODENT**<br>82-1(a) | -A NOEL was not established<br>-Lack of characterization of the test substance or incorrectly reported<br>-Lack of clinical chemistry and/or lack of histopathology |
| **90-DAY FEEDING - NON-RODENT**<br>82-1(b) | -Reporting deficiencies<br>-Lack of characterization of the test substance<br>-A NOEL was not established<br>-An investigational parameter missing<br>-Information on the pilot study and other problems associated with dose level selection |
| **21-DAY DERMAL TOXICITY**<br>82-2 | -Lack of characterization of the test substance<br>-Raw data analyses incomplete or missing<br>-A systemic NOEL was not established<br>-Inadequate percentage of body surface area exposed in each dose group<br>-Insufficient number of dose levels tested |
| **90-DAY DERMAL TOXICITY**<br>82-3 | -Lack of characterization of the test substance<br>-A systemic NOEL was not established<br>-Incomplete/missing raw animal data analyses<br>-Insufficient number of dose levels tested<br>-Poorly controlled test environment |
| **CHRONIC FEEDING/ ONCOGENICITY - RATS**<br>83-1(a) and 83-2(a) | -Missing histopathology information<br>-Missing information in study reports<br>-MTD was not achieved<br>-Missing historical control data<br>-Lack of characterization of the test substance<br>-Deficiencies in reporting the study data |
| **ONCOGENICITY - MICE**<br>83-2(b) | -Histopathology information missing<br>-MTD was not achieved<br>-Lack of historical control data<br>-Information missing in study reports<br>-Lack of characterization of the test substance<br>-Deficiencies in reporting of study data |

**DEVELOPMENTAL TOXICITY - RODENTS**
83-3(a)

-Missing historical controls
-Lack of characterization of the test substance
-Information missing or requiring clarification of the laboratories methods
-Information missing or requiring clarification of the laboratories results
-A NOEL was not established
-Statistical problems
-Did not use conventional assessments for skeletal or visceral examinations

**DEVELOPMENTAL TOXICITY - NON-RODENTS**
83-3(b)

-Clarification of laboratory procedures or interpretation of the data
-Individual maternal or fetal data missing
-Missing historical controls
-Lack of characterization of the test substance
-Excessive maternal toxicity
-A NOEL was not established
-Statistical problems

**REPRODUCTION**
83-4

-Information missing from laboratory results
-Lack of characterization of the test substance
-Information missing or requiring clarification of laboratory methods or results
-Missing historical controls
-A NOEL was not established due to effects at the lowest dose tested
-Low fertility and/or inadequate number of animals were used per dose level
-A NOEL was not established in the absence of reproductive effects

**MUTAGENICITY TESTING**
84-2

**A) Gene mutations**

-Purity, batch numbers, stability, or analytical concentration information missing
-MTD issue, no range-finding study; inadequate high dose; no evidence of toxicity at any dose; insufficient (or no) cytotoxicity and limit-dose level (5000 μg/plate) not reached and/or test substance not tested up to solubility limits
-Insufficient (or inappropriate) tester strains used in Ames assays
-Tester strains not verified in Ames assays
-For mammalian cells in culture, harvest time was not determined by cell-cycle analysis
-Missing protocol; missing raw data
-The results were "equivocal"
-Only 1 dose was administered

**B) Structural chromosome aberrations**

1) Tests include: Mouse micronucleus assay and in vivo mammalian cytogenics assay with rodent bone marrow

-Dose levels were too low or no explanation of why this is the maximum attainable concentration; no or low cytotoxicity indicating that an insufficient level of test substance was transported to the target tissue (MTD issue)
-Purity or test substance missing; analysis of concentration in solution; or analysis of stability missing
-Less than 3 dose levels were performed
-Missing: individual clinical signs, body weight data, or raw data (e.g., route of administration, slide code information, strain or source of animals)
-Inappropriate sampling times, or cells were not exposed during the entire hematopoietic cycle

2) Dominant lethal - rats or mice

-MTD issue
-No evidence that the test material reached the target cells
-Low pregnancy rates
-Missing positive control

**C) Other genotoxic effects**

1) Tests include: in vitro unscheduled DNA synthesis (UDS) in rat hepatocytes, the human Hela cell line, human fibroblasts, or rat kidney cells

-No analytical or stability data to define the test substance concentration, purity, or solubility in solution question
-Missing: raw data, results for metabolic activation, background frequencies for UDS, protocol; or that insufficient data was presented to support conclusions
-MTD issue, no evidence of cytotoxicity, missing dose selection data
-High cytoplasmic grain count in solvent control; repeat study with different rat hepatocyte preparation, or lower cytoplasmic background, or high cytoplasmic and nuclear grain counts, or counts were not provided
-Duplicate cultures were not performed

2) Tests include: In vitro transformation assay: a) BALB/3T3 (mouse); (B0 C3H10T 1/2 (mouse)

-Only one test dose used, or MTD issue
-Purity and stability of test substance

3) Tests include: In vivo sister chromatid exchange (SCE): (a) chinese hamster; (b) rat bone marrow

-MTD issue; dose selection not supported by range-finding study; no cytotoxicity was indicated at highest dose
-No analytical data to support test substance stability, concentration, or missing test substance purity
-Missing procedural descriptions
-Inadequate statistical analyses

**METABOLISM**
85-1

-Inadequate or missing data on identification of metabolites
-Improper methodology or dosing regimen
-Inadequate number of animals were used in the dose groups
-No individual animal data
-Improper reporting
-Inadequate or missing tissue residue analysis data
-Testing at only one dose level
-Only one sex of animal used
-Lack of an intravenous dose group
-No collection of $^{14}CO_2$

**DERMAL PENETRATION** -Incomplete/missing data evaluation
85-2

-Improper test substance preparation/application
-Raw data missing and incomplete summary tables
-No signed quality assurance statement
-Missing purity or concentration of test substance

(3) Environmental Fate

Rejection rates for environmental fate are characterized on the following five graphs. Key implications that might be drawn from these graphs include:

(1) overall rejection rates in environmental fate appear to have gone down significantly;

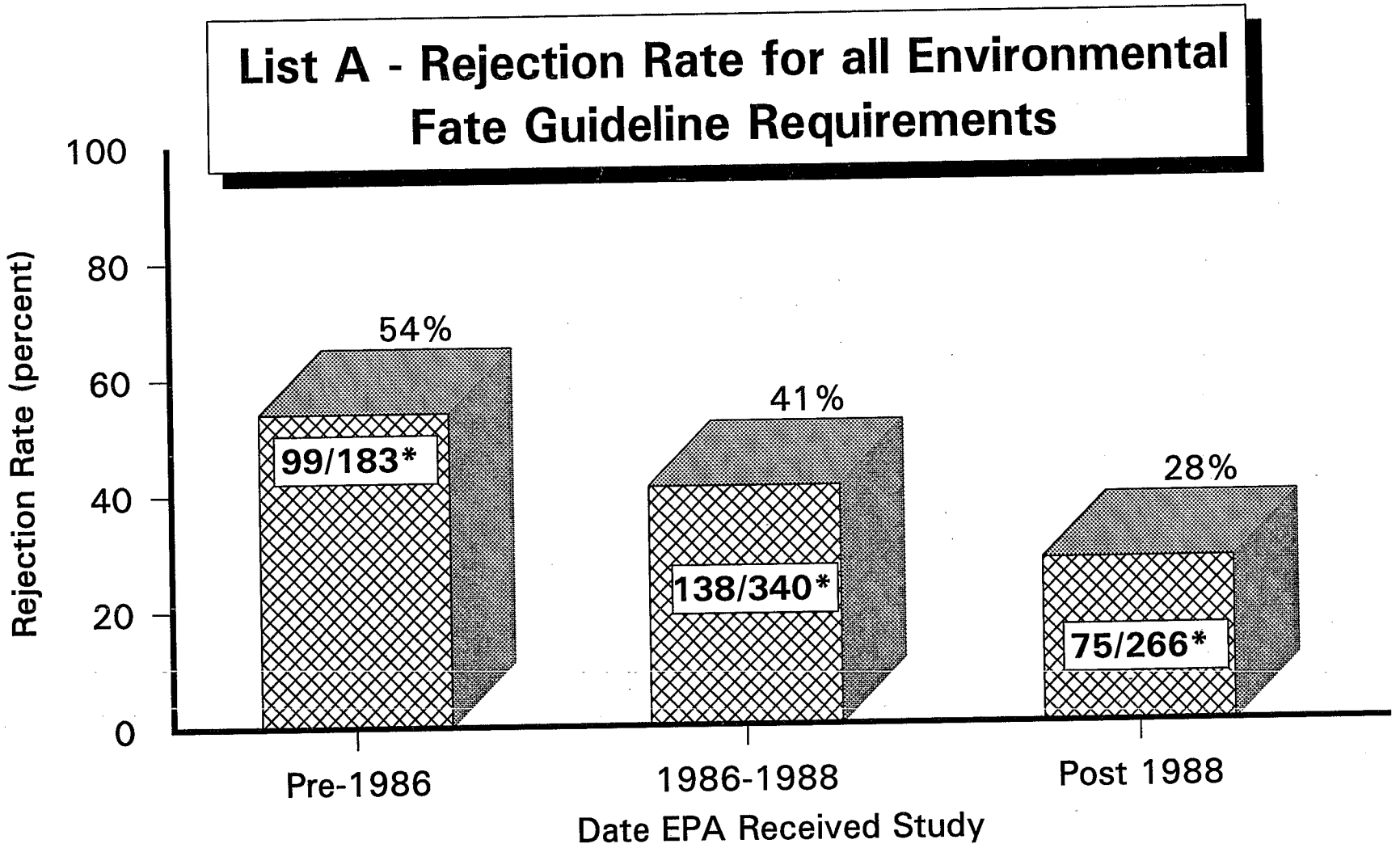
(2) the photodegradation - water (161-2), photo-degradation - soil (161-30, leaching (163-1), terrestrial field dissipation (164-1) and aquatic field dissipation (164-2) guidelines have shown a continuous and substantial decline in their rejection rates;

(3) for the aerobic soil metabolism (162-1), anaerobic soil metabolism (162-2), confined crop rotation (165-1) and bioaccumulation in fish (165-4) guidelines, the rejection rate trends do not indicate substantial improvement;

(4) all of the guidelines examined still have high rejection rates when compared to the goal of reducing all rejection rates to 10% or less;

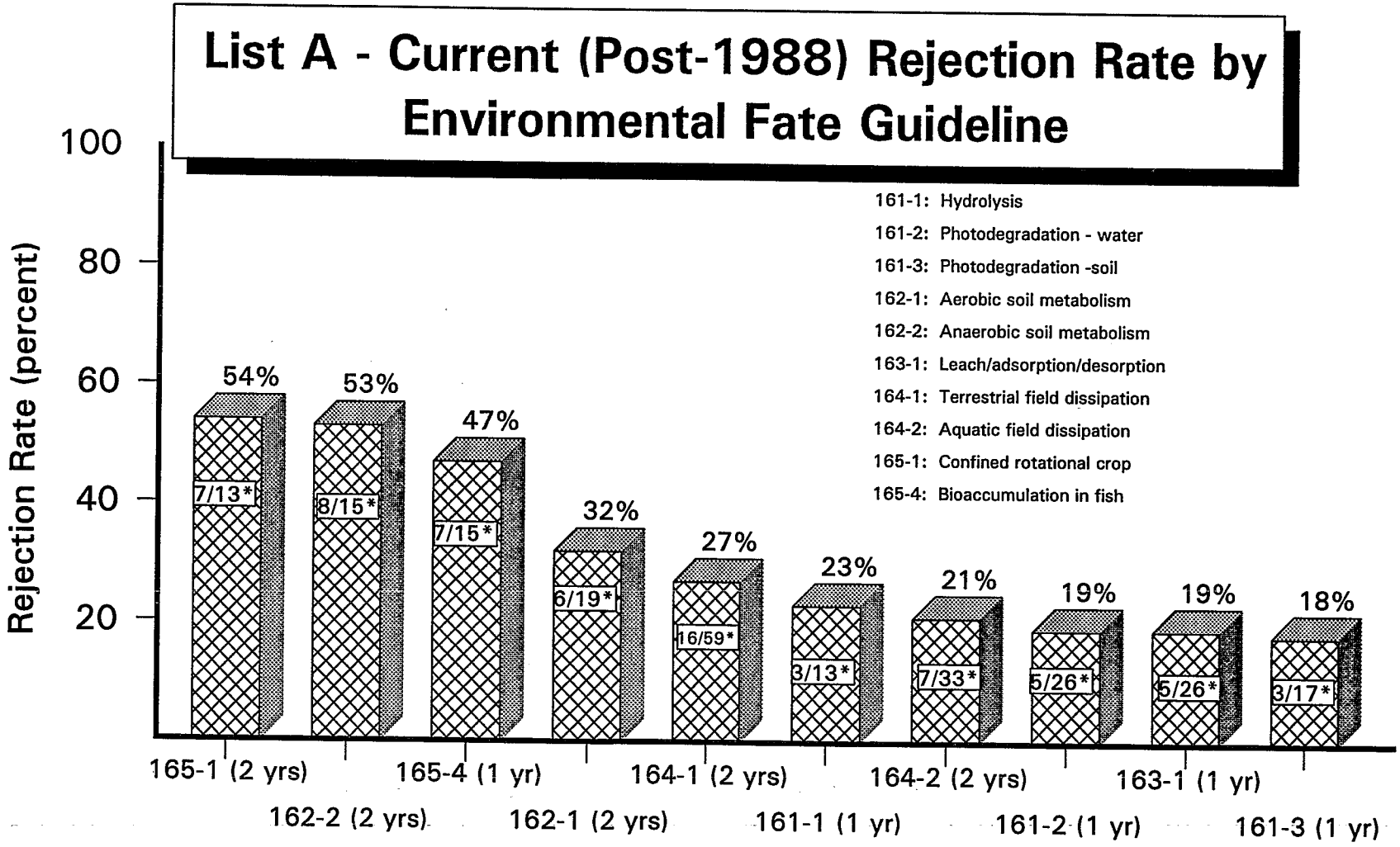
Discussions between Agency and registrant scientists revealed that the tight time frames and limited resources imposed by FIFRA 88 forced industry to start studies before results from other pertinent studies had been reviewed and approved by the Agency. Consequently, rejection factors in the earlier lab studies cascaded down into the subsequent field study causing it to be rejected as well.

Figure 1




* - number of rejected studies/total number of studies reviewed

Figure 2

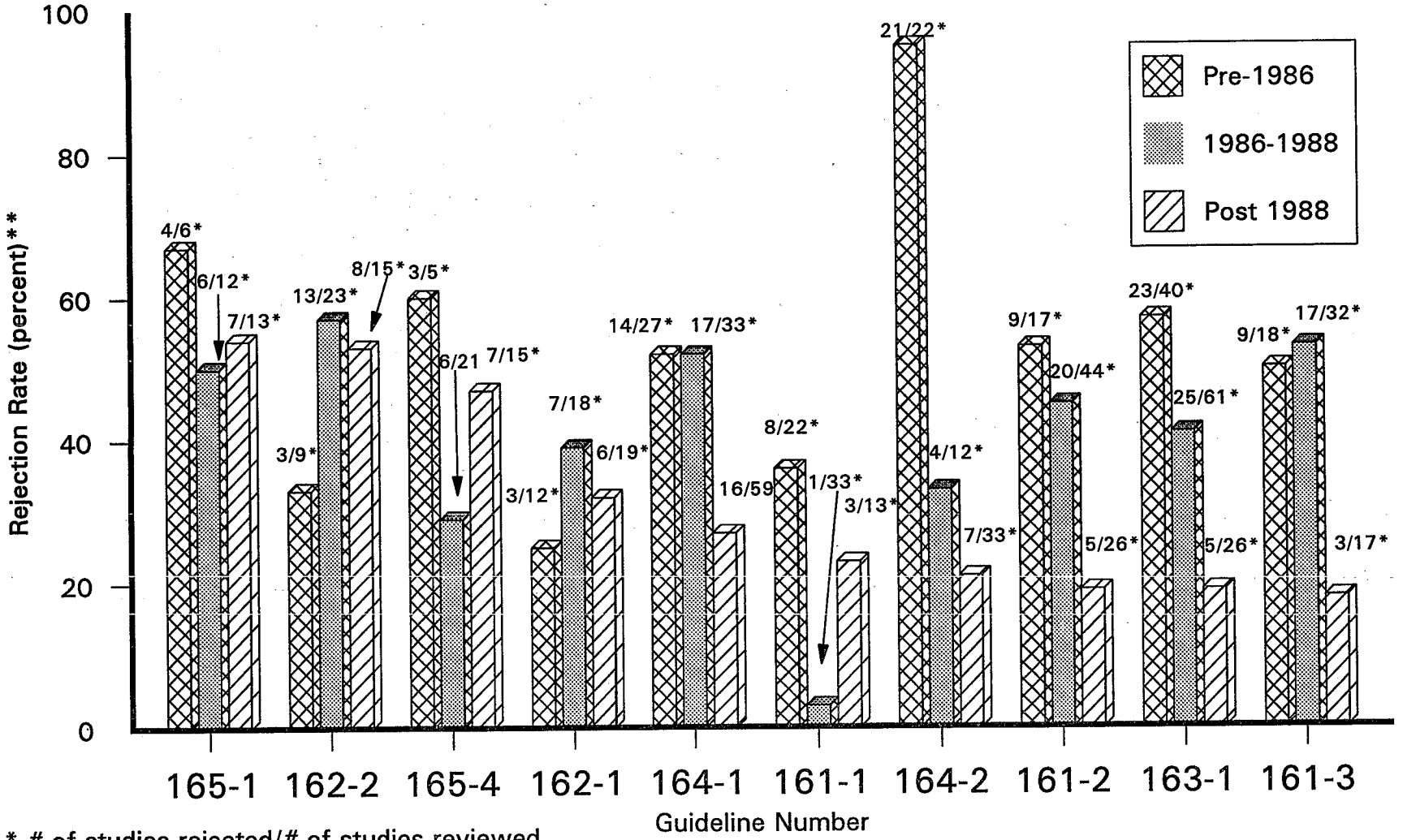



* - # of studies rejected/# of studies reviewed
( ) # of years to complete study

Note: Insufficient data to evaluate:161-4,162-3,162-4,163-2,163-3,164-3,164-4, 165-5,165-2,165-3,165-5,166-1,166-2,166-3,167-1,167-2,201-1,202-1

Figure 3

# List A - Environmental Fate Rejection Rate Prior to 1986 to Post 1988




* # of studies rejected/# of studies reviewed

Note: Insufficient data to evaluate:161-4,162-3,162-4,163-2,163-3,164-3,164-4, 165-5,165-2,165-3,165-5,166-1,166-2,166-3,167-1,167-2,201-1,202-1

Figure 4

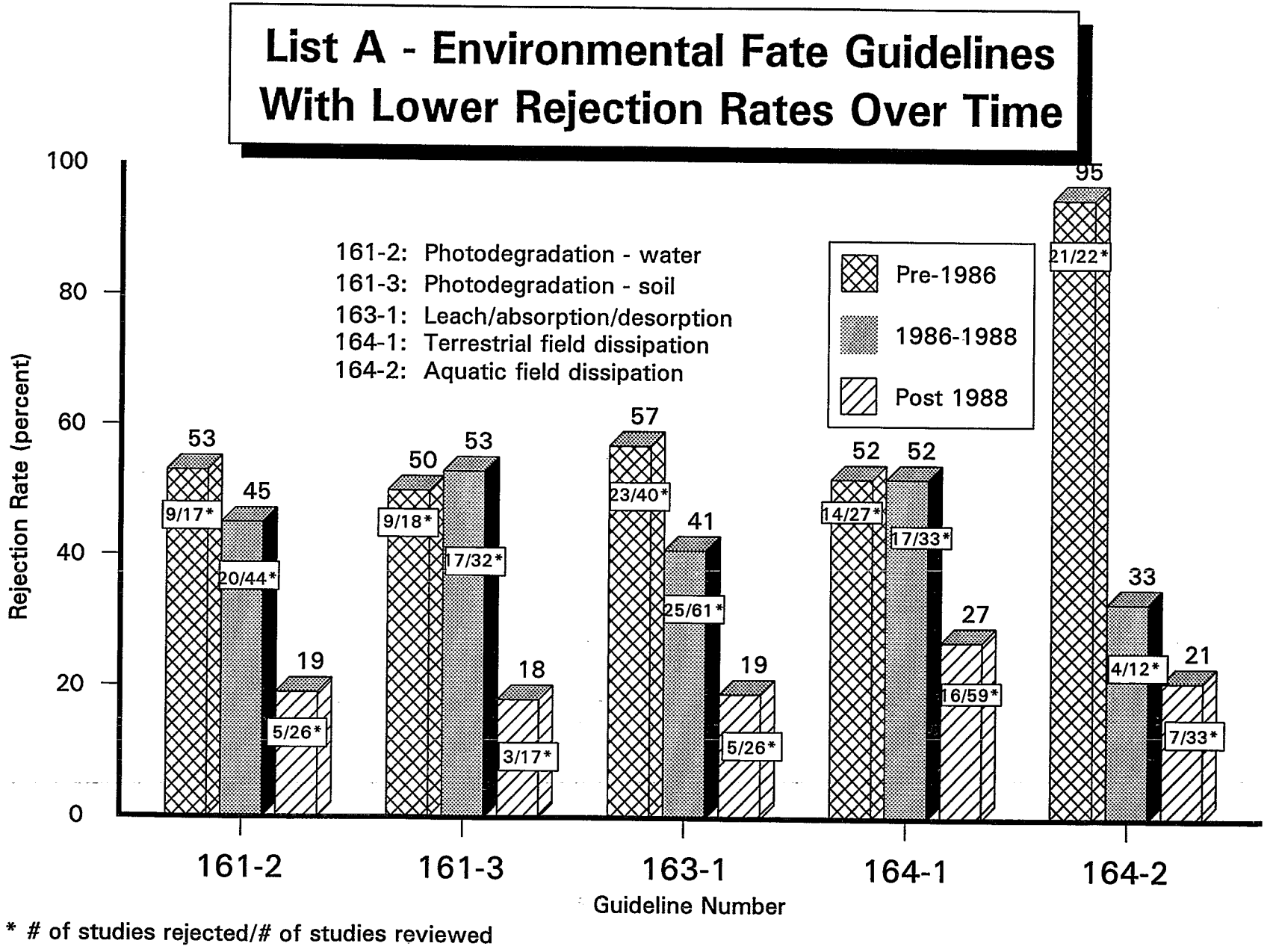
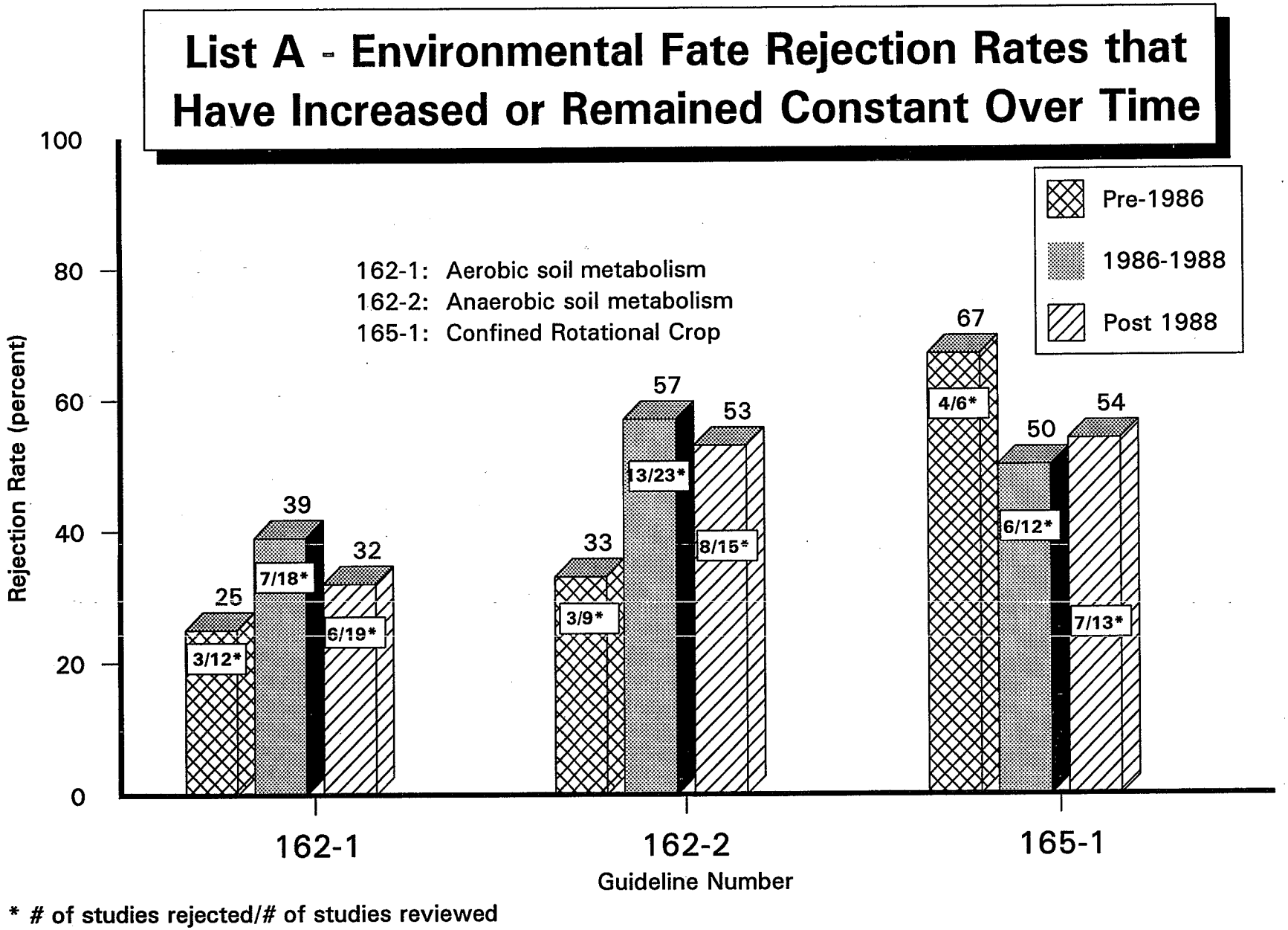

List A - Environmental Fate Guidelines With Lower Rejection Rates Over Time
161-2: Photodegradation - water
161-3: Photodegradation - soil
163-1: Leach/absorption/desorption
164-1: Terrestrial field dissipation
164-2: Aquatic field dissipation
Pre-1986
1986-1988
Post 1988
Rejection Rate (percent)
100
80
60
40
20
0
53
45
19
9/17*
20/44*
5/26*
50
53
18
9/18*
17/32*
3/17*
57
41
19
23/40*
25/61*
5/26*
52
52
27
14/27*
17/33*
16/59*
95
33
21
21/22*
4/12*
7/33*
161-2
161-3
163-1
164-1
164-2
Guideline Number
* # of studies rejected/# of studies reviewed

Figure 5


List A - Environmental Fate Rejection Rates that Have Increased or Remained Constant Over Time
Pre-1986
1986-1988
Post 1988
162-1: Aerobic soil metabolism
162-2: Anaerobic soil metabolism
165-1: Confined Rotational Crop
Rejection Rate (percent)
100
80
60
40
20
0
25
39
32
3/12*
7/18*
6/19*
33
57
53
3/9*
13/23*
8/15*
67
50
54
4/6*
6/12*
7/13*
162-1
162-2
165-1
Guideline Number
* # of studies rejected/# of studies reviewed

# SUMMARY TABLE OF REJECTION FACTORS - ENVIRONMENTAL FATE

## 161-1 HYDROLYSIS STUDY

1) A material balance was not provided
2) The study was not conducted in the dark.
3) The study duration and number of sampling intervals were insufficient to establish the decline and half-life.
4) It was not specified that the buffer solutions were sterile; before, it could not be determined if degradation was due to hydrolysis or biotic processes.
5) The test substance was not characterized.
6) The incubation temperature was not maintained.
7) Insufficient data were presented to support the reported conclusion.
8) Degradation curves and regression analysis were not provided.

## 161-2 PHOTODEGRADATION STUDIES IN WATER

1) The light source was not adequately characterized and was not compared to sunlight.
2) Degradates were not identified.
3) The material balances were incomplete.
4) The test solutions were not buffered and the pH of the water was not reported.
5) The analytical methodology was incomplete and no raw data was provided to support the conclusions.
6) The sampling protocol was inadequate.
7) The temperatures of the test solutions were not reported.
8) Volatilization was neither measured nor controlled.
9) A photosensitizer was used as the co-solvent.
10) It was not specified that the test solutions were sterile.
11) The study was terminated before the half-life of the test substance was established or before 30 days.
12) The coefficients of determination for the data used to determine the half-lives were very poor.
13) The stability of the pesticide under refrigeration was not addressed.

## 161-3 PHOTODEGRADATION ON SOIL

1) The material balance was incomplete.
2) Volatilization was neither measured nor controlled.
3) Artificial light source was not similar to natural sunlight.
4) The test substance was not technical grade or pure.
5) Raw data were not provided.
6) The incubation temperature was not provided.
7) Degradates were not identified.
8) The test was not performed on soil.
9) The treatment rate was not reported.

## 161-4 PHOTODEGRADATION IN AIR

1) The pesticide degradation in the vapor phase could not be distinguished from degradation that occurred in material adsorbed to the sides of the glass container.
2) Air samples were never analyzed separately from nonvaporized pesticide.
3) The material balance was low.
4) High percentages of unidentified material were reported.
5) The registrant did not measure the vapor pressure at the temperature the study was conducted.
6) The analytical method was inadequate.
7) The spectrum of the artificial light source was not similar to that of natural sunlight.
8) A photosensitizer was present in the primary stock solution.
9) No raw data was submitted.

## 162-1 AEROBIC SOIL METABOLISM

1) Residue identification was incomplete.
2) The material balance was inadequate.
3) The study was conducted for an inadequate length of time to establish the patterns of formation and decline.
4) Purity of the test substance was not specified.
5) The experimental design was inadequate to assess the metabolism in soil.
6) The incubation temperature was not reported.
7) The soil textures could not be confirmed because the soils were not classified using the USDA Soil Textural Classification System.
8) The analytical methodology was incomplete and no raw data were provided to support conclusions.
9) The raw data examined did not support the half-life reported by the registrant.
10) Degradate characterization data were presented as percent of recovered rather than percent of applied.

## 162-2 ANAEROBIC SOIL METABOLISM

1) Residue identification was incomplete.
2) The material balance was inadequate.
3) The purity of the test substance was not specified.
4) The storage stability data were not provided, although the raw data indicate that both soil samples and extracts were stored prior to analysis.
5) Degradates present in small concentrations were not identified.
6) The experimental design was inadequate to accurately assess the degradation under anaerobic conditions.
7) The length of frozen storage was not specified. Frozen storage stability data are required to confirm that the residues were stable.
8) Method detection limits were not provided.
9) Large discrepancies existed in the data for duplicate samples collected after anaerobic conditions were established. The data, therefore, cannot be used reliably to calculate the rate of degradation in soil under anaerobic conditions.
10) The study was conducted for an inadequate length of time to establish the patterns of formation and decline of the pesticide under anaerobic conditions. The study should have been conducted for 60 days.
11) No raw data were provided to support the conclusions.
12) A complete description of the test water, including the pH and dissolved oxygen content, was not provided.
13) The soil was not classified according to the USDA Soil Textural Classification System.

## 162-3 ANAEROBIC AQUATIC METABOLISM

1) The sampling protocol was inappropriate because it contained too few sampling intervals and was inadequate to establish the half-life for the pesticide.
2) The pesticide residues were quantified using a chemically nonspecific analytical method. No attempt was made to characterize the pesticide residues in soil and water matrices.
3) Material balances were incomplete.
4) Degradates were not identified.
5) The test substance was not technical grade or purer.
6) The test water was not characterized. Foreign soils were not completely characterized and may not have been typical of those in the United States. The soil must be representative of that found at an intended use site.

## 162-4 AEROBIC AQUATIC METABOLISM

1) The sampling schedule was inadequate.
2) Material balances were incomplete.
3) Residues were incompletely characterized.
4) The test water was not characterized.

## 163-1 LEACHING/ADSORPTION/DESORPTION

1) Degradates were not identified.
2) The test soils were autoclaved prior to conducting the study.
3) The material balance was incomplete.
4) Soils and sediments were incompletely characterized.
5) Desorption of a major degradate was not addressed.
6) Foreign soils were used which may not be typical of soils in the United States.
7) Kd values (values of soil/water relationships) were not reported.
8) The desorption phase was done serially, with incomplete removal of the supernatant at each step.
9) The soil texture could not be confirmed because the soil was not classified using the USDA Soil Textural Classification System.
10) It was not established that the equilibrium time used was sufficient for the soil:solution slurries to reach equilibrium.
11) The bioassay methods used in the study were not acceptable analytical techniques.
12) Soil used in the study was not prepared properly.
13) Test solution was not characterized.
14) The data were presented on a percentage basis with no actual concentrations.

## 163-2 LABORATORY VOLATILITY

1) Analytical methodology was insufficient.
2) The study was not carried out over a long enough period of time to clearly define a volatility decline curve.
3) The soil was not analyzed immediately after treatment. Therefore, the application rate was not confirmed.
4) No material balance was reported or the data reported was insufficient.
5) Not all major formulation categories were tested.
6) The soil was autoclaved before the test.
7) The rate of volatilization was incorrectly calculated and could not be determined with the information provided.
8) The experiments were not replicated.

163-3 FIELD VOLATILITY

1) The soil data were inadequate to confirm the application rate.
2) Data on soil samples was not provided.
3) The description of experimental conditions were insufficient.

164-1 TERRESTRIAL FIELD DISSIPATION

1) The original concentration of the pesticide was not reported or the reported application rate was not confirmed in soil samples taken immediately post-treatment.
2) The pattern of formation and decline of the degradates was not addressed.
3) The sampling was not done to depths sufficient to define the extent of leaching.
4) Characterization of residues was not provided for all sites or the soil was not analyzed for the correct residues or for all residues.
5) Complete soil characteristics and field test data were not provided.
6) The analytical methodology was insufficient to identify the residues (in one case, the analytical method could not distinguish between the parent and its degradates).
7) The data were too variable to accurately assess the dissipation of the test substance.
8) The freezer storage stability data were inadequate.
9) The maximum label rates were not used, and the soil incorporation procedure recommended on the label was not followed.
10) The formulation and method of application were not specified.
11) The plants were harvested after application and the time of harvest was not given.
12) Pretreatment samples were contaminated.
13) More than one pesticide was applied to the crop.
14) The experiment was conducted at only one site instead of the two recommended in the Guidelines.
15) The method of detection limit and recovery efficiencies were not reported.

164-2 AQUATIC FIELD DISSIPATION

1) Complete field test data were not provided.
2) The analytical methodology was insufficient to determine the residue.
3) The material balance was insufficient.
4) Data were too variable to assess dissipation.

164-3 FORESTRY FIELD DISSIPATION

1) The data provided were either insufficient or too variable to accurately establish a pattern of dissipation of a chemical and its primary degradate in a forest environment.
2) The sampling protocol was inadequate.
3) The application rate was not reported.
4) No storage stability data were provided to confirm that samples did not degrade prior to analysis.
5) Field test data were incomplete.

165-1 CONFINED ACCUMULATION IN ROTATIONAL CROPS

1) The residues in soil were not characterized.
2) The length of freezer storage of the crops was not reported and no freezer storage stability data were provided.
3) The study application rate does not reflect normal or maximum use rates and the application rate was not confirmed.
4) The test substance was less than analytical grade.
5) The supporting raw data were not provided.

165-2 FIELD ACCUMULATION IN ROTATIONAL CROPS

1) The source of pesticide residues in control samples of both crops and soils were not verified.
2) There was a large degree of variability in the data with no explanation provided.
3) Residues in soil were not analyzed.
4) Planting to harvest intervals were not provided.
5) The field test data were incomplete.
6) The test substance was not characterized.

165-4 ACCUMULATION IN FISH

1) The analytical methodology was insufficient to detect the residue.
2) Some degradates present in small concentrations in edible and non-edible fish tissues were not identified and/or quantified.
3) The study on the effects of storage on the analytical results of samples was not completed.
4) Data on the concentration of the parent and its degradates in the exposure water were not submitted.
5) Mortality and growth/weight patterns of fish throughout the study were not provided.

(4) Ecological Effects

Rejection rates for ecological effects are characterized on the following six graphs. Key implications that might be drawn from these graphs include:

(1) overall rejection rates in ecological effects appear to have gone down significantly, but current rates remain high;

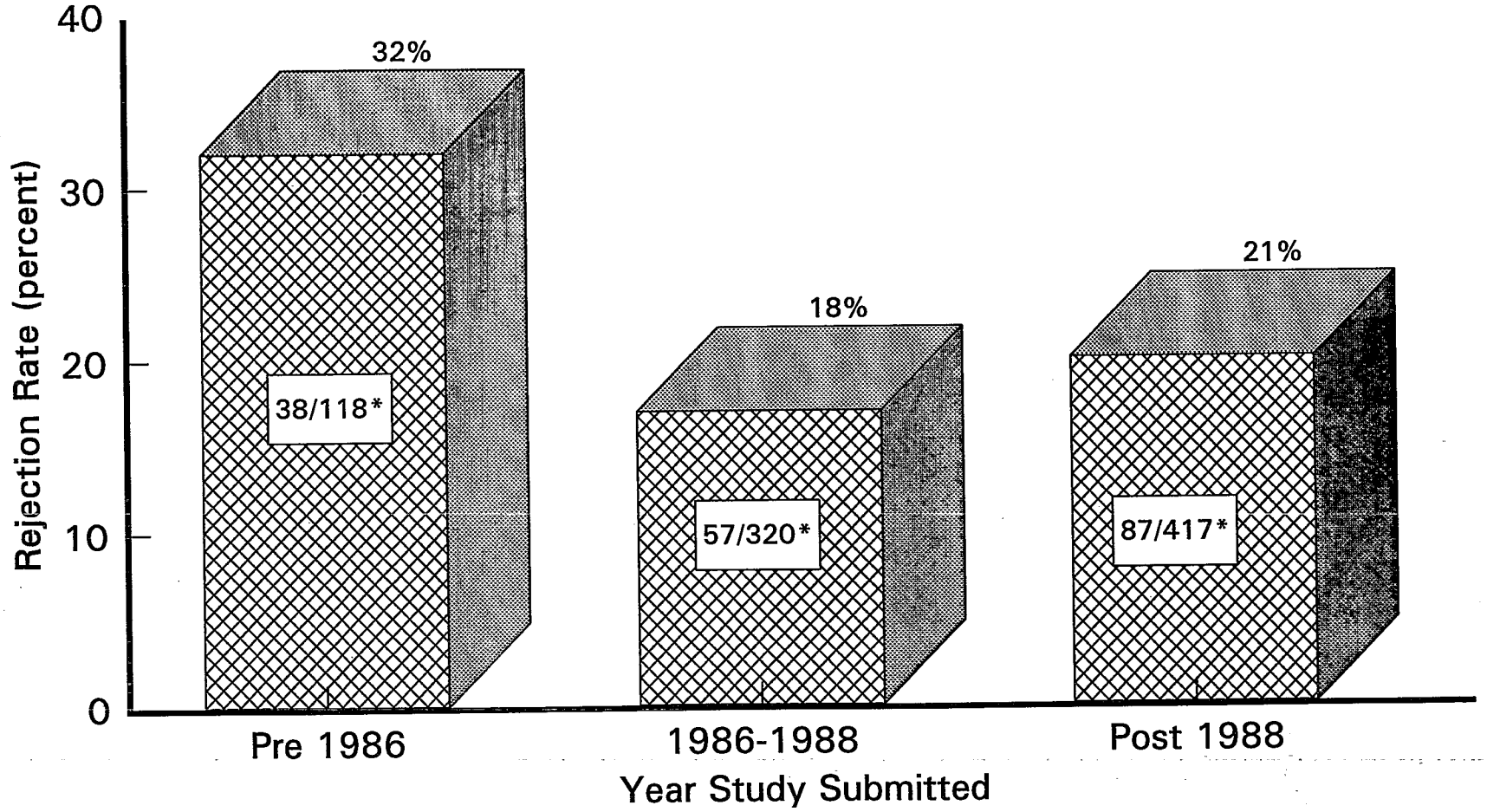
(2) for both avian and aquatic reproduction studies, the high rejection rates indicate significant problems;

(3) five of the six fish acute toxicity studies have current (post-1988) rejection rates greater than 10%;

(4) four acute toxicity guidelines-71-1, acute avian oral; 72-1C, acute toxicity trout; 72-2, acute toxicity Daphnia; and 72-3B, acute toxicity mollusk-have shown encouraging and consistent reductions in their rejection rates over time.

Figure 1

# List A Rejection Rates for all Ecological Effects Guideline Requirements

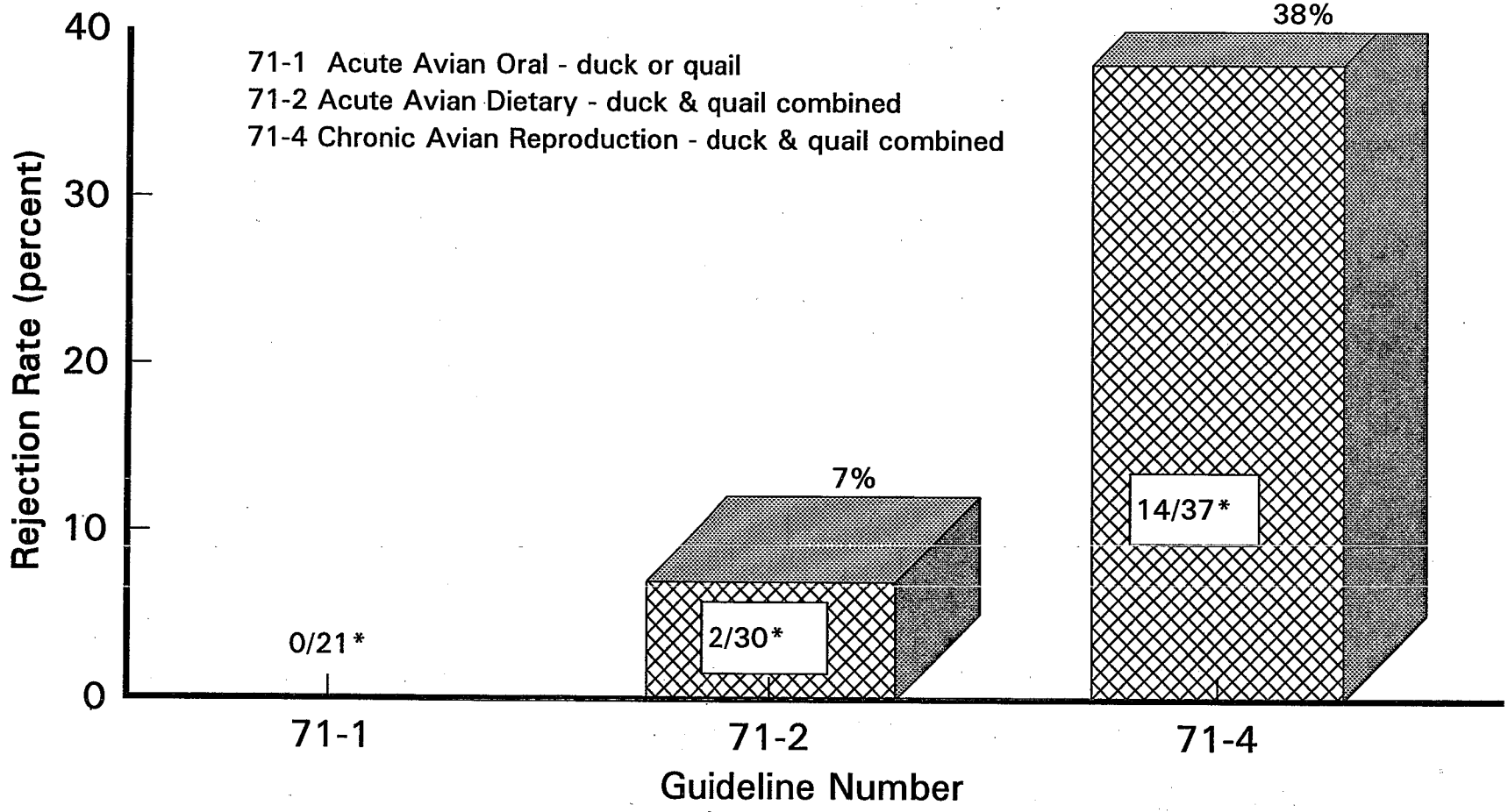



* # rejected studies/# studies reviewed

Note: Rejection rates include List A studies reviewed as of 12/1/92, but do not include studies submitted prior to Registration Standards.

Figure 2

# List A - Current (Post 1988) Rejection Rates by Guideline - Avian Acute and Reproduction Toxicity

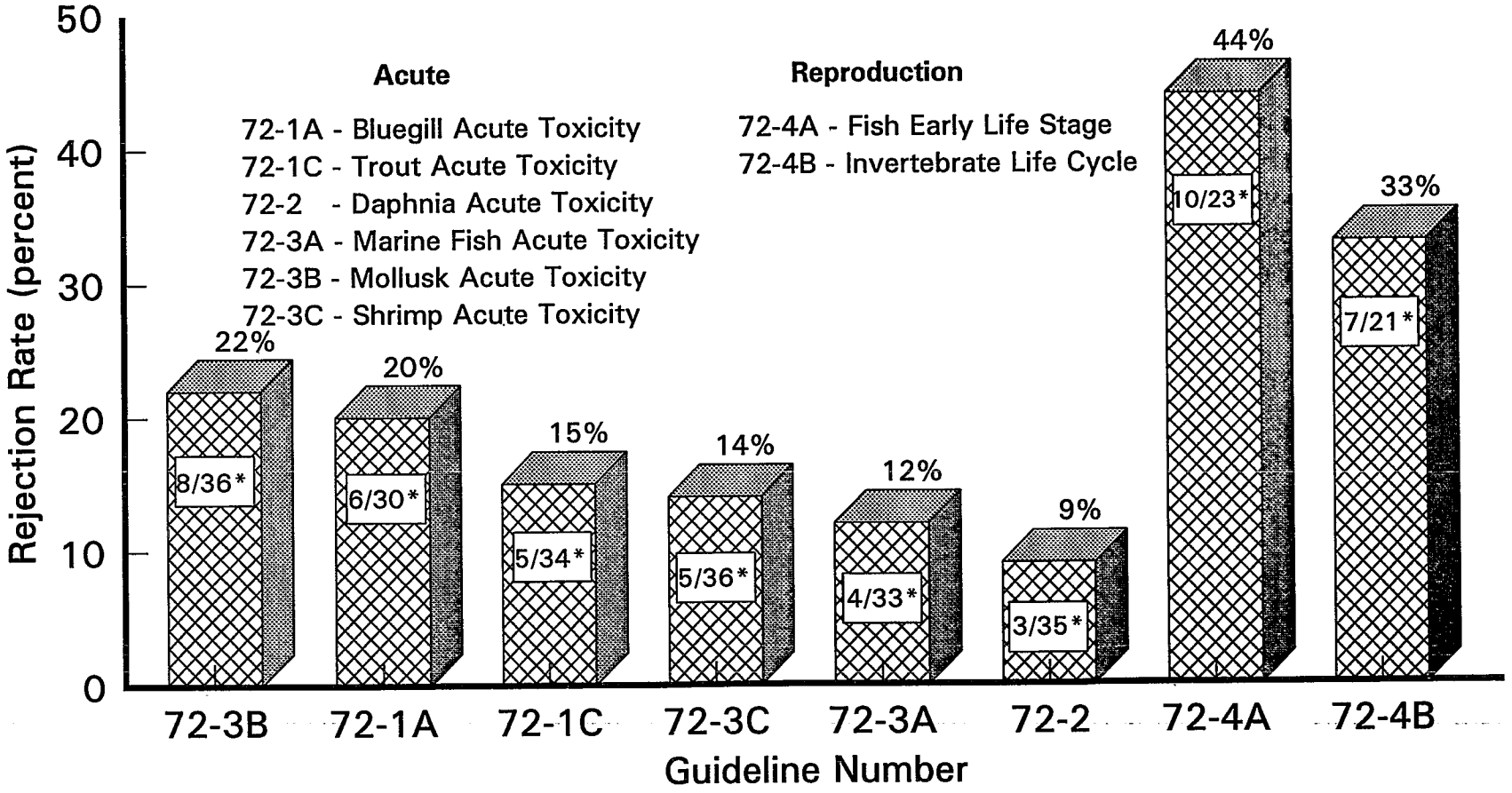



* # rejected studies/# studies reviewed

Note: Insufficient data to evaluate 71-3 and 71-5

Figure 3

# List A - Current (Post 1988) Rejection Rates by Guideline - Fish Acute and Reproduction Toxicity

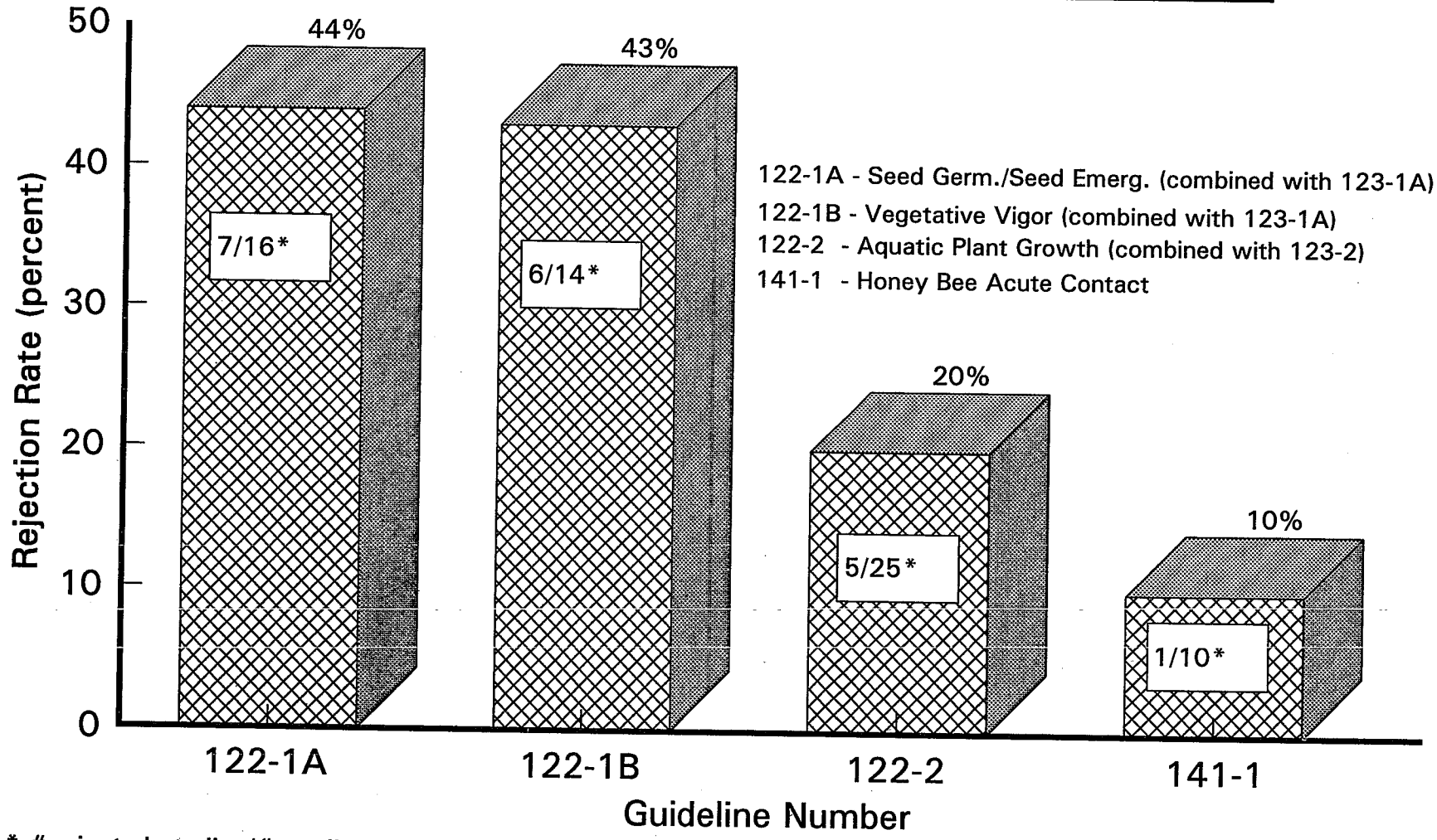



* # rejected studies/# studies reviewed

Note: Insufficient data to evaluate 72-5, 72-6, and 72-7

Figure 4

# List A - Current (Post 1988) Rejection Rates by Guideline - Other




* # rejected studies/# studies reviewed

Note: Insufficient data to evaluate 124-1, 124-2, and 141-2

Figure 5

# List A - Ecological Effects Guidelines with Lower Rejection Rates over Time

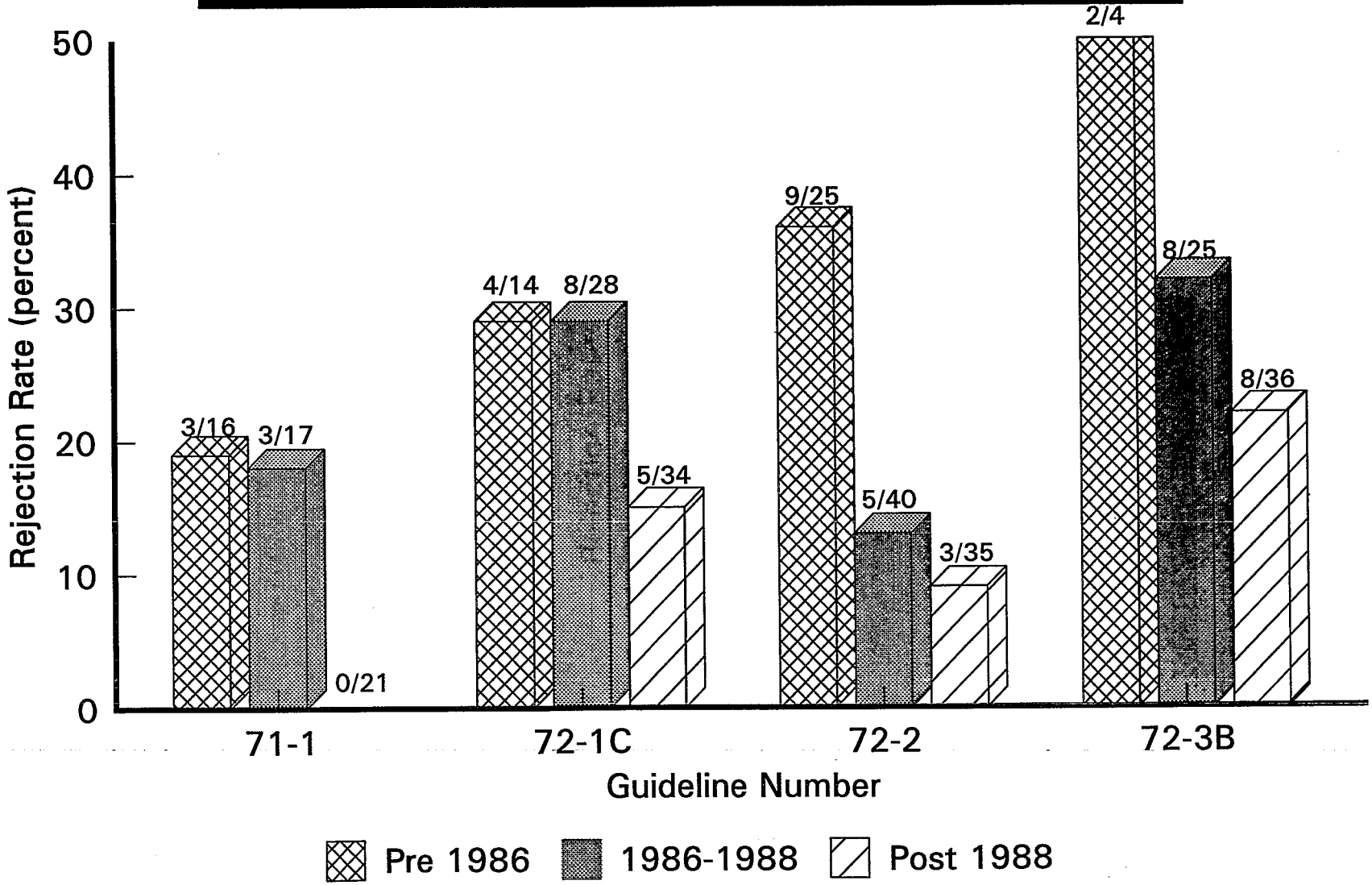
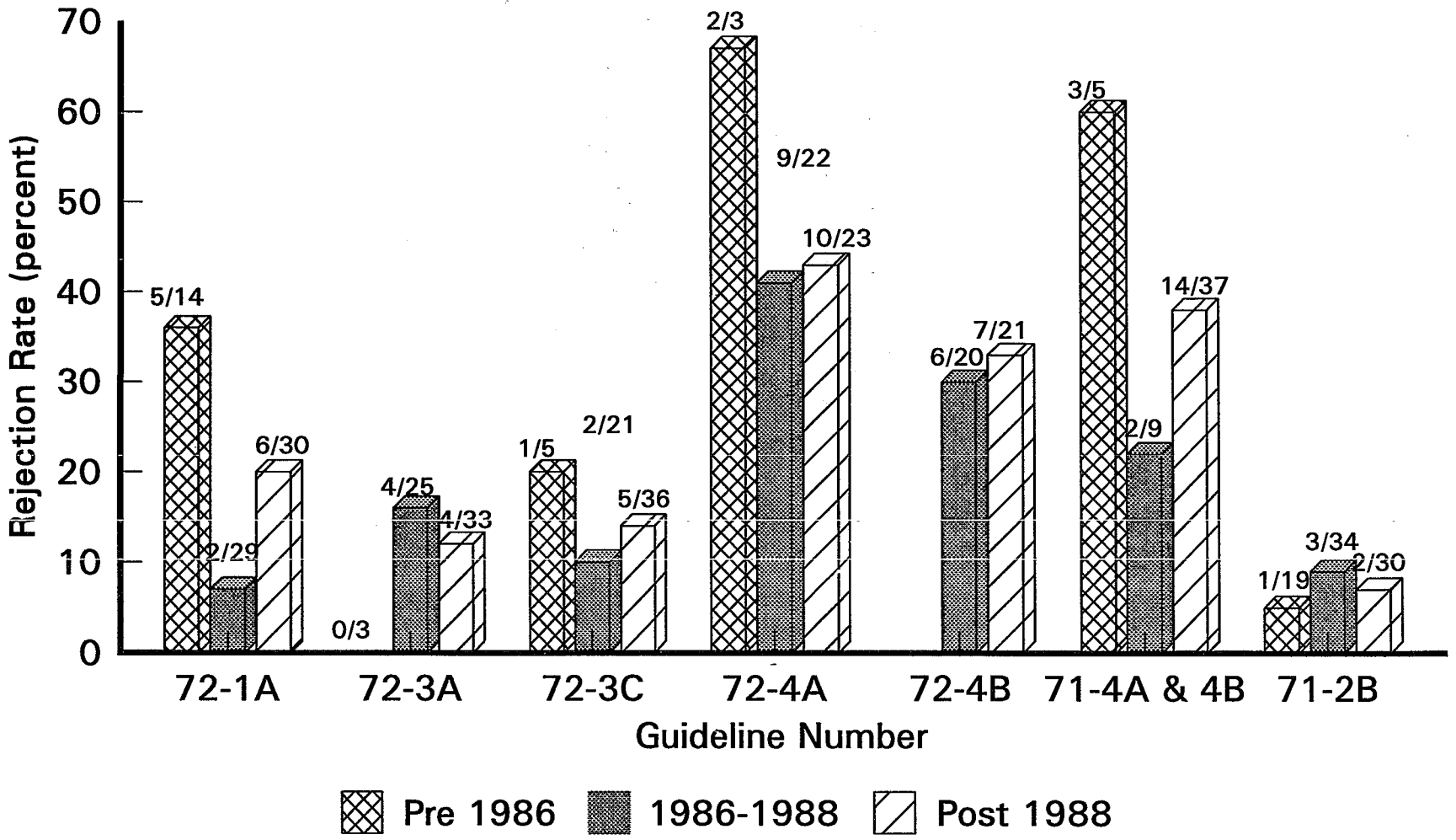


Figure 6

# List A - Ecological Effects Guideline Rejection Rates Without Consistent Improvement Over Time



# Summary Table of Rejection Factors - Ecological Effects

| GUIDELINE | REJECTION FACTORS |
|---|---|
| **Avian Oral $LD_{50}$ 71-1** | -Failure to establish a valid $LD_{50}$ value with corresponding 95 % confidence limits or an $LD_{50}$ greater than 2000 mg/kg.<br>-Use of a "split-dosing" procedure.<br>-Fasting period prior to dosing not specified. |
| Avian Dietary $LC_{50}$ 71-2 | -Mortalities attributed to interactions between animals (rather than to test chemical), when such interactions were not observed in the controls.<br>-High variability in the measured test concentrations in the test diet.<br>-Test material was not technical grade.<br>-$LC_{50}$ not established when testing at dose levels < 5000 ppm a.i.<br>-Variation in test concentration and/or failure to adequately justify the variations. |
| **Freshwater Fish $LC_{50}$ (Bluegill) 72-1** | -Concentration level < 100 mg/l, not high enough to produce an $LC_{50}$.<br>-Aeration of test chambers.<br>-Biological loading of test vessels twice the recommended amount.<br>-Test substance purity not identified.<br>-Inappropriate test species and/or test species not clearly identified.<br>-Fish fed during the exposure period.<br>-Minimum limit of detectability, or the minimum quantifiable limit, not defined quantitatively.<br>-Test concentrations variability limit > 1:5.<br>-Levels of lead, iron and aluminum present in dilution water higher than recommended.<br>-No solvent control.<br>-Results for some test concentrations obtained from tests conducted after the definite study.<br>-Not all test solutions measured at 96 and 0 hours.<br>-No control group for the inert/carrier ingredient component of the formulation.<br>-Acclimation period half that recommended. |

| GUIDELINE | REJECTION FACTORS |
|---|---|
| **Freshwater Fish $LC_{50}$ (Rainbow) 72-1** | -All of the rejection factors listed above for guideline 72-1, Bluegill.<br>-Fish acclimation period overlapping with the definite study period.<br>-Contamination of the controls with test chemical.<br>-Low recovery of test chemical from the stock solutions.<br>-Fish weights exceeding the recommended range.<br>-Test temperature exceeding the recommended for the test species.<br>-Biological loading of the system greater than recommended.<br>-Fish mortality during the acclimation period higher than recommended.<br>-Supersaturation of oxygen. |
| **Acute $LC_{50}$ Freshwater Invertebrates 72-2** | -Organisms not randomly distributed to test vessels.<br>-Water temperature not monitored.<br>-Chemical analyses (concentration levels) not performed on test solutions.<br>-No control group for the inert/carrier ingredient component of the formulation.<br>-Minimum limit of detectability, or the minimum quantifiable limit, not defined quantitatively.<br>-Test concentrations variability limit > 1.5.<br>-Not all test concentrations measured at 0 and 48 hours.<br>-Levels of lead, iron and aluminum present in dilution water higher than recommended.<br>-Percent of a.i. of the test formulation not identified.<br>-Photoperiod not as recommended.<br>-Raw temperature data not provided.<br>-Use of dechlorinated water as a portion of the dilution water. |
| **Wild Mammal Toxicity 71-3** | -Diet preparation method not adequate.<br>-Improper animal caging, as indicated by extensive cannibalism. |
| **Avian Reproduction Quail 71-4** | -Percent of cracked eggs in the control higher than in treatment groups.<br>-Data discrepancies:<br>=inappropriate photoperiod;<br>=reasons for administration of medication not provided;<br>=total number of data points not included in statistical evaluation. |
| **Avian Reproduction Duck 71-4** | -Data discrepancies:<br>=inappropriate photoperiod;<br>=inappropriate egg collection procedures;<br>=low overall fertility of control birds. |
| **Acute $LC_{50}$ Estuarine and Marine Organisms Fish 72-3D** | -Unexplained variations in concentrations.<br>-Concentration level < 100 mg/l, not high enough to produce an $LC_{50}$.<br>-Dissolved oxygen levels lower than recommended.<br>-Analytical determination of the concentration in the test vessels not provided. |

| GUIDELINE | REJECTION FACTORS |
|---|---|
| **Acute $LC_{50}$ Estuarine and Marine Organisms Mollusc 72-3B and E** | -Insufficient new shell growth in control oysters.<br>-Insufficient dosage levels to produce a reliable $LC_{50}$.<br>-Raw data on shell deposition not provided.<br>-Aeration of test chambers without chemical analyses of test solutions.<br>-Dissolved oxygen levels lower than recommended. |
| **Acute $LC_{50}$ Estuarine and Marine Organisms Shrimp 72-3C** | -Test substance purity not identified.<br>-Chemical analysis of test solutions concentration not performed.<br>-Type and quantity of solvent used not provided.<br>-Solubility needed to achieve $LC_{50}$ not obtained. |
| **Fish Early Life Stage 72-4** | -Mortality too high at all concentrations.<br>-Raw data not submitted.<br>-Survival rate in the control group lower than recommended.<br>-Erratic results in measured test concentrations. |
| **Aquatic Invertebrate Life Cycle 72-4** | -Raw data not submitted.<br>-NOEL values for reproduction and growth cannot be established from study results.<br>-Survival rate in the control group lower than recommended.<br>-Adults' growth (length and weight) not measured quantitatively. |
| **Invertebrate Life Cycle Estuarine Species 72-4** | -Reproduction rates too low to be statistically analyzed.<br>-Adult body lengths not measured at the end of the study.<br>-Feeding rate below the recommended daily ration.<br>-Raw data not provided. |

(5) Occupational and Residential Exposure

There were no rejected mixer/loader applicator studies in the reregistration data base that could be used in the rejection rate analysis. For post-application/reentry studies the data base indicated 18 out of 71 reviewed studies were coded as rejected (a 25% rejection rate). This number overestimates the number of studies that have to be repeated because an examination of some of these rejected studies indicated reasons for rejection that could be rectified without repeating the study. Rejection factors are provided below.

Summary Table of Rejection Factors

| Guideline | Rejection Factor |
|---|---|
| 132-1A, 132-1B, | -Inadequate or complete lack of quality assurance/quality control data |
| 133-3, 133-4 | -Did not provide meterological data. |
| | -Used inappropriate toxicological end points and transfer coefficients when calculating reentry levels. |
| | -Insufficient sampling intervals. |

In summary the following generic factors can account for most of the study rejections:

(1) inadequate QA/QC by data doers;

(2) inadequate or conflicting guidance to address rejection factors provided by the Agency;

(3) changing criteria for conducting acceptable quality studies by the Agency; and

(4) inadequate time frames provided in legislation to conduct studies leading to cascading rejection factors.

RESULTS TO DATE

To what extent this project succeeds in reducing rejection rates can be quantitatively assessed. However, what studies to assess and when to assess them isn't so straightforward.

Including all studies reviewed from the date of this project would not provide an accurate assessment of the impact of this effort on reducing rejection rates because many of the studies reviewed today have been sitting in OPP's backlog of unreviewed studies for years and were completed before this project was even initiated. This project clearly has had no impact on the acceptability of those studies already submitted and in the unreviewed study backlog at the time this project was initiated, and including them in an assessment would only bias the results.

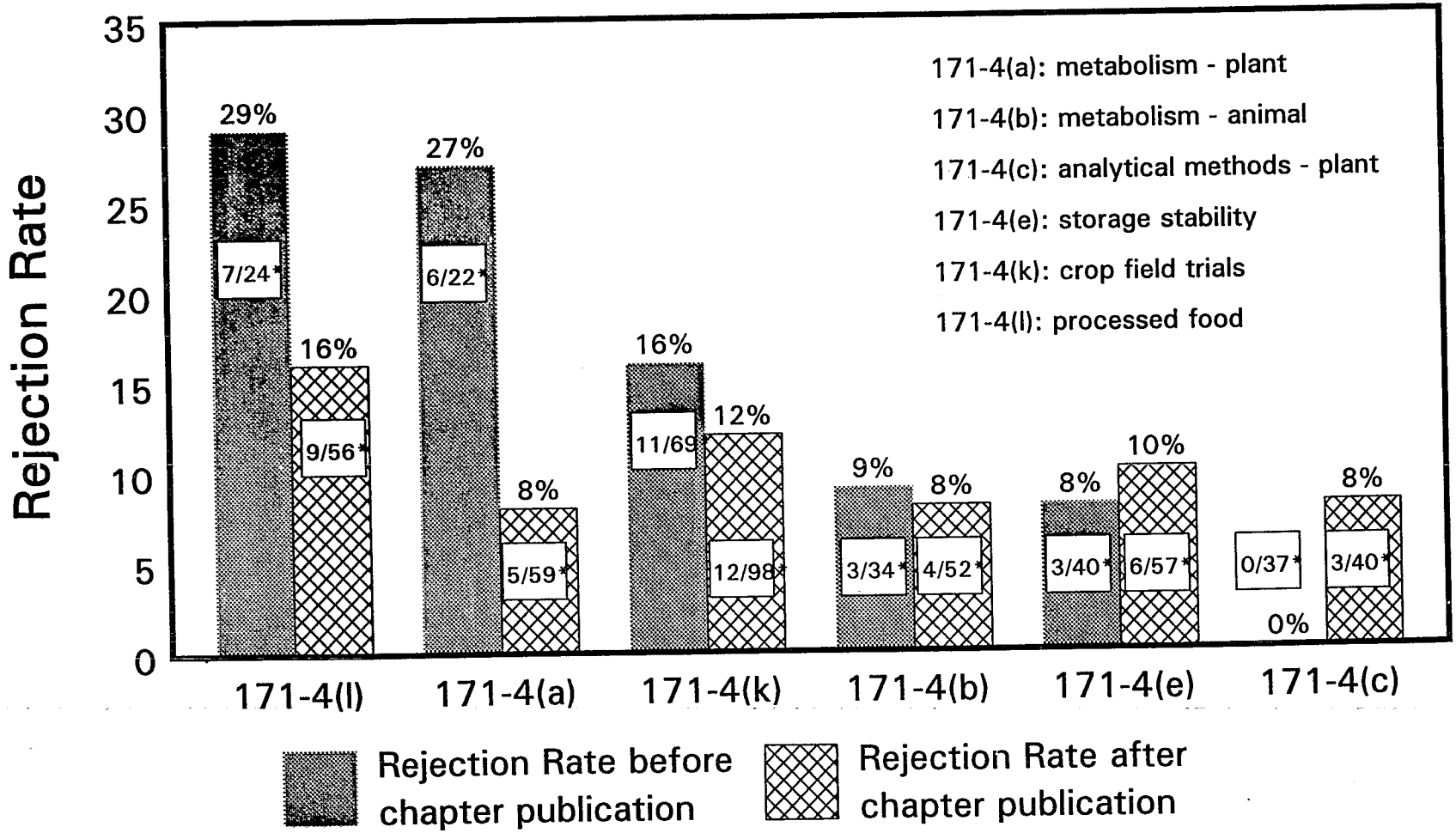
Counting only those studies received and reviewed since the publication of the relevant rejection rate chapter is also problematic. First, some of the "solutions" that have been implemented to reduce the occurrence of the rejection factors can only be implemented at the initiation of a study. Therefore, studies already ongoing at the time of publication of a rejection rate chapter may not have benefitted from the contents of the chapter even though the study was submitted after the chapter's publication date. Secondly, for a given scientific discipline, the rejection rate chapter is not the only source of "solutions". For some rather difficult problems uncovered in the assessment, more elaborate follow-up guidance have been warranted. For example, in residue chemistry four additional follow-up guidances have been published since the initial publication of the residue chemistry rejection rate chapter in July 1992.

Residue chemistry is the only discipline that can be evaluated at this time to determine what impact this project has had in reducing rejection rates. The residue chemistry rejection rate chapter was the first chapter published, and enough time has elapsed for a sufficient number of new studies to be submitted and reviewed. Only studies submitted after the July 1992 chapter publication date were considered. The results reported below should be considered preliminary because many of the follow-up guidance were not published for a considerable amount of time after July 1992. The last residue chemistry follow-up guidance was published in June 1994.

The following chart compares rejection rates before and after chapter publication. The food processing study [171-4(1)] had the highest rejection rate in residue chemistry - 29%. Since publication of the rejection rate chapter, the rejection rate has been cut almost in half to 16%. For the plant metabolism study [171-4(a)], the rejection rate has been significantly reduced from 27% to 8%. This is especially important since rejection factors from the plant metabolism study often cascaded

# Residue Chemistry Rejection Rates

## Before and After Chapter Publication




All List A studies reviewed since June 1992

down into subsequent studies causing them to be rejected as well. The crop field trial study [171-4(k)] rejection rate has only been reduced slightly from 16% to 12%. Since this is the single most frequently levied data requirement, a greater reduction in the rejection rate is needed. The current results, however, are not surprising since the follow-up guidance addressing the most critical rejection factor for this study (inadequate geographical representation) was only published in June 1994. Sufficient time has not elapsed to assess the impact of this additional guidance. The analytical methods study [171-4(c)] rejection rate increased from 0 to 8%. Since no rejected studies appeared in the sample used for the residue chemistry rejection rate analysis, no attention was given to this guideline requirement. Should this rejection rate continue to increase, an assessment of the rejection factors would be warranted in the future.

In addition to working with Agency scientists to resolve underlying factors causing study rejection, registrants also initiated internal, company-specific efforts to identify factors or processes within their own companies that warranted improvement. Seventeen companies and the IR-4 agreed to undertake this effort. They are: Rhone Poulenc, Agrevo, ICI, Ciba, Miles, Monsanto, Rohm & Haas, Dupont, Cyanamid, DowElanco, Valent, Uniroyal, FMC, ISK Biotech, Hazleton, ABC Laboratories and ETI.

Only two companies have submitted reports at this time. DowElanco had a company rejection rate of approximately 52% as of November 1991. According to Craig Barrow, DowElanco's regulatory manager, the company initiated changes to increase (1) the individual accountability of the registration managers and lab study directors for the outcomes of their studies and (2) increase the communication between company and agency scientists. DowElanco implemented an "on time, right the first time" performance standard for their personnel. A quarterly report is distributed widely throughout the company to track progress. It includes each study, the name of the study director and registration manager responsible for it, when it was submitted to the Agency, whether it was submitted on time, and the review outcome - accepted or rejected (rejected includes both studies that have to be repeated as well as studies that are upgradeable).

At the same time DowElanco sought to improve the communication between company scientists performing the studies and Agency scientists responsible for reviewing them. Company scientists were brought to Washington for meetings with the Agency, and ARI was used to fund a visit by Agency scientists to a DowElanco lab to view and discuss how new neurotoxicity studies should be carried out.

In 1993 66% of DowElanco's studies (137 out of 207) for reregistration were submitted on time and 70% of the studies reviewed (189 out of 270) were acceptable. For 1994, 94% (136 out of 145) were submitted on time, and 80% of the studies reviewed (139 out of 174) were acceptable. In three years DowElanco's rejection rate performance has improved from one of the worst in the industry to one of the best.

Rhone Poulenc had a company specific rejection rate of 45% in 1990. According to Peg Cherny, Rhone Poulenc's regulatory manager, the company:

(1) developed a study review outcome data base and tracking system that includes each study, when it was submitted to the Agency and whether it was accepted or rejected (rejected includes studies that must be repeated as well as studies that are upgradeable);

(2) identified problematic studies which had the highest rejection rates for Rhone Poulenc;

(3) initiated process improvement teams in areas of concern to reengineer core processes where necessary;

(4) reorganized scientists into different functional teams to better utilize resource and experience base and shifted more personnel into critical groups where shortages existed;

(5) brought in company scientists to meet with Agency scientists to improve communication and understanding;

(6) developed a centralized library of EPA guidance documents easily accessible to company scientists; and

(7) consolidated the number of independent labs that Rhone Poulenc contracted studies out to as part of the company's lab management strategy to improve their quality and timeliness.

In 1991, 69% of Rhone Poulenc's studies that were reviewed were acceptable. In 1992, 73% of the studies submitted and reviewed were acceptable. In 1993, 88% were acceptable, and in 1994, 87% were acceptable. In four years Rhone Poulenc's rejection rate performance improved to one of the best in the industry.

RECOMENDATIONS:

The following recommendations are warranted:

1. The Agency shall continue to monitor periodically the rejection rates for individual guideline studies. Any rejection rate that persists above 10% should warrant future management/industry attention.

2. Individual companies should closely monitor their own rejection rates to avoid the huge costs associated with repeating rejected studies and potentially missing a growing reason for new chemicals. Companies should be able to reduce rejection rates to 10% or less.

3. It is imperative that the Agency review its backlog of unreviewed studies because (1) many of these studies were submitted prior to this rejection rate project, (2) are more likely to be rejected than new studies that have benefitted from the lessons learned from this project, and (3) could cause significant delays in completing the reregistration program.

## Footnotes

1. Based on a November 1991 Rejection Rate Report for Lists A & B.

2. By multiplying the number of hours to review a study by the probability that the study will be rejected, the expected additional review hours due to future rejected studies can be predicted. This algorithm was applied to all unsatisfied data requirements for each chemical case as of 1993. 300 out of the remaining 324 chemical cases were covered. By list, the estimated number of additional review hours is:

| List | Additional Review Hours |
|---|---|
| List A | 17,026 |
| List B | 46,454 |
| List C | 29,881 |
| List D | 4,429 |
| | 97,790 |

3. The upper bound estimate of $1.2 billion was derived in the following manner: (1) From a June 1991 Workload Management Report, a sample of 87 List A cases was used to determine the average number of unsatisfied guidelines per case, which was 57 studies. From a sample of 86 List B cases the average number of unsatisfied guidelines per case was 101. From a sample of 30 cases from Lists C & D (15 cases from each list) the average number of unsatisfied guidelines per case was 77 studies for List C and 43 studies for List D. (2) An industry survey Cost of Conducting Studies for Pesticide Registration (June 1993) provided individual costs of conducting 105 different studies (not including product chemistry studies) which totaled $15,445,977. The average cost per study was $147,104. By multiplying the average cost per study by the average number of unsatisfied studies per case and then multiplying that product by the number of cases per list, the total cost of conducting the studies in reregistration is estimated.

| List | Avg # of studies per case | * | Avg Cost per study | * | # of cases per list | = | Cost per list |
|---|---|---|---|---|---|---|---|
| A | 57 | | $147,104 | | 151 | | $1,266,124,128 |
| B | 101 | | $147,104 | | 104 | | $1,545,180,416 |
| C | 77 | | $147,104 | | 81 | | $ 917,487,648 |
| D | 43 | | $147,104 | | 69 | | $ 436,457,568 |
| | | | | | | | $4,165,249,760 |

By multiplying the $4,165,249,760 sum by the historical rejection rate of 30%, the upper bound estimate of $1.2 billion for repeating rejected studies is derived.

A lower bound estimate is warranted because rejection rates have been falling during reregistration. By multiplying the cost to conduct the study by the current rejection rate for that study, the expected additional costs to repeat rejected studies can be estimated for each chemical. By list the expected additional cost estimates are:

| List | Expected Additional Costs to Repeat Studies |
|---|---|
| A | $ 66,973,119 |
| B | $284,627,203 |
| C | $186,629,365 |
| D | $ 22,490,265 |
| | $560,719,652 |

The lower bound estimate is approximately $0.6 billion to repeat rejected studies.

4. Based on November 1991 rejection rate reports for individual companies.

5. An actual List A chemical is used here as an example of how the probabilistic RED schedule is generated for this chemical. On the chemical profile sheet (on next page) the unsatisfied study requirements (as of March 1993) are listed in columns 1& 2. The unsatisfied guidelines are aggregated into three groups - all one-year studies, all two-year studies and all four-year studies. Column 3 contains the due date for each study. Columns 4 & 5 contain the study-specific rejection rates and the corresponding acceptance rate (1.0 - rejection rate). The probability that all of the one-year studies will be acceptable is the joint product of their individual acceptance rates. This joint product is 0.16 (in column 5 below the one-year studies) and is referred to as Q1. The probability that all of the two-year studies will be acceptable is the joint product of the individual acceptance rates for the two-year studies. This joint product, referred to as Q2, is 0.76. Similarly, the probability that all of the four-year studies will be acceptable is the joint product of the individual acceptance rates for the four-year studies. This joint product, referred to as Q3, is 0.71. The probability that this List A RED will be issued on time is the joint probability that all studies will be acceptable which can be expressed as:

(1) Probability of RED issued on time = (Q1*Q2*Q3) = (.16*.76*.71) = .08

The probability that one or more one-year studies will be rejected is 1 - Q1. Therefore, the probability of a one-year delay in the RED is the joint probability of one or more one-year studies being rejected and all two and four-year studies being acceptable. This can be expressed as:

# CHEMICAL PROFILE - LIST A CHEMICAL

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| CHEMICAL NAME: | List A RED | | | | | | | |
| As of: | 3/24/93 | | | | | | | |
| | | | | | | | | |
| GUIDELINE NUMBER | GUIDELINE NAME | DUE DATE | REJECTION RATE | ACCEPTANCE RATE | AGENCY HRS TO REVIEW | REGISTRANT COST | Expected FTE hrs to Repeat | Expected Cost to Repeat |
| | | | | | | | | |
| 1-year studies | | | | | | | | |
| 72-4(a) | Early life stage fish | Nov-93 | 0.44 | 0.56 | 8 | 65,311.50 | 3.52 | 28,737.06 |
| 72-4(b) | Invertebrate life cycle | Nov-93 | 0.33 | 0.67 | 6 | **67,500.00 | 1.98 | 22,275.00 |
| 161-1 | Hydrolysis | UR | 0.23 | 0.77 | 8 | 66,443.50 | 1.84 | 15,282.01 |
| 161-2 | Photodegradation - water | Mar-93 | 0.19 | 0.81 | 8 | 81,138.00 | 1.52 | 15,416.22 |
| 161-3 | Photodegradation - soil | Mar-93 | 0.18 | 0.82 | 8 | 90,108.00 | 1.44 | 16,219.44 |
| 163-1 | Leach/adsorb/desorption | UR | 0.19 | 0.81 | 15 | 66,445.00 | 2.85 | 12,624.55 |
| | | | | | | | | |
| *Product of Acceptance Rate (Q1)* | | | | 0.16 | | | | |
| | | | | | | | | |
| | | | | | | | | |
| 2-year studies | | | | | | | | |
| 82-2 | 21-day dermal rabbit/rat | UR | 0.04 | 0.96 | 17.25 | 62,600.00 | 0.69 | 2,504.00 |
| 82-5(b) | 90-day neurotox - mammal | Nov-94 | 0.07 | 0.93 | 22 | 160,913.00 | 1.54 | 11,263.91 |
| 171-4(a) | Storage stability | May-93 | 0.08 | 0.92 | 78.4 | 29,190.00 | 6.27 | 2,335.20 |
| 81-8-SS | Acute neurotox - rat | Nov-93 | 0.07 | 0.93 | 90 | 104,825.00 | 6.30 | 7,337.75 |
| | | | | | | | | |
| *Product of Acceptance Rate (Q2)* | | | | 0.76 | | | | |
| | | | | | | | | |
| | | | | | | | | |
| 4-year studies | | | | | | | | |
| 83-1(b) | Chronic - dog | Nov-93 | 0.00 | 1.00 | 110.25 | 455,749.00 | 0.00 | 0.00 |
| 83-4 | 2-generation repro - rat | Nov-93 | 0.02 | 0.98 | 19 | 402,524.50 | 0.38 | 8,050.49 |
| 166-3 | Groundwater monitoring | *UR | 0.28 | 0.72 | 360 | 2,776,666.50 | 100.80 | 777,466.62 |
| | | | | | | | | |
| *Product of Acceptance Rate (Q3)* | | | | 0.71 | | | | |
| | | | | | | | | |
| | | | | Probabilistic | LSDD + 1 year | | 15.18 | 31,491.35 |
| Probability on time (Q1*Q2*Q3) | Nov-95 | Nov-95 | FY96 | 0.08 | | | | |
| Probability of 1 yr delay (1-Q1)Q2*Q3 | May-97 | May-97 | FY97 | 0.46 | | | | |
| Probability of 2 yr delay (1-Q2)Q3 | May-98 | May-98 | FY98 | 0.17 | | | | |
| Probability of 4 yr delay (1-Q3) | May-00 | May-00 | FY00 | 0.29 | | | | |
| | | | | | | | | |
| TOTAL | | | | 1.00 | | | | |
| | | | | | | | | |
| ASSUMPTIONS: | | | | | | | | |
| 1. Reserved studies are not included | | | | | | | | |
| 2. Studies conducted by the Spray Drift Task Force are not included | | | | | | | | |
| 3. Craven DCIs are not included since the data has not yet been called in | | | | | | | | |
| 4. The RED delay date is based on an additional 1 1/2 years | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| KEY: | | | | | | | | |
| WP = Waiver Pending | | | | | | | | |
| UR = Unreviewed study | | | | | | | | |
| * = Due date for 166-1 study is not considered as the last study due date | | | | | | | | |
| ** = Contractor cost estimate taken from "Terms of Clearance for Phase 4 & 5 of Reregistration" ICR #1504 OMB #2070-0107 (5/8/91) | | | | | | | | |
| *** = All Data In | | | | | | | | |

(2) Probability of a one year delay in the RED = [(1-Q1)*Q2*Q3]=[(1-.16)*.76*.71]= .46

The probability that one or more two-year studies will be rejected is 1-Q2. The probability of a two year delay in the RED is the joint probability of one or more two-year studies being rejected and all four year studies being acceptable. This can be expressed as:

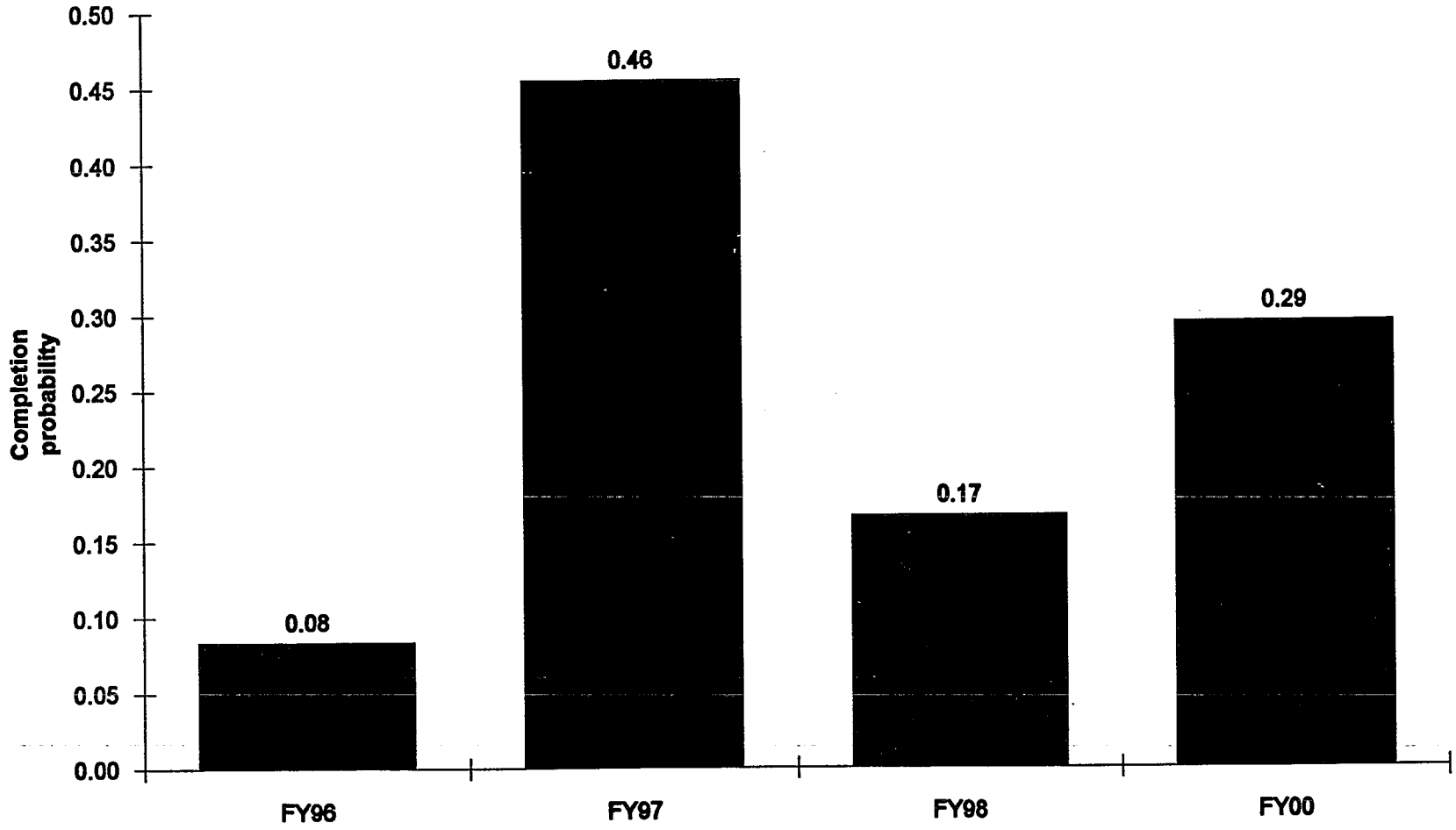
(3) Probability of a two year delay in the RED = [(1-Q2)*Q3] = [1-.76)*.71 = .17

The probability that one or more four-year studies will be rejected is 1-Q3. Therefore, the probability of a four year delay in the RED can be expressed as:

(4) Probability of a four year delay in the RED = 1 - Q3 = 1 - .71 = .29

This list A chemical, then, has a 8% probability of being completed on time in FY 96, a 46% probability of being one year late and being completed in FY97 , a 17% probability of a two year delay and being completed in FY98, and a 29% probability of a four-year delay and being completed in FY2000 as depicted in the following graph.

## Probabilistic RED Schedule for the List A RED



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