United States
Environmental Protection
Agency

Office of Pesticides
and Toxic Substances
Washington DC 20460

EPA-560/4-81-002
February 1981

Toxic Substances

EPA

Cost Analysis Methodology and Protocol Estimates:

OECD Minimum Pre-Market Data Test Protocols

EPA-560/4-81-002

COST ANALYSIS METHODOLOGY AND PROTOCOL ESTIMATES:

OECD Minimum Pre-Market Data Test Protocols

by
Janis C. Kurtz
Allan Cohen

Project Officers:
Joye Akridge
Sammy K. Ng

OFFICE OF REGULATORY ANALYSIS
OFFICE OF TOXIC SUBSTANCES
Washington, DC. 20460

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES AND TOXIC SUBSTANCES
Washington, DC. 20460

PREFACE

The attached document is a contractor's study performed under the supervision and review of the Office of Pesticides and Toxic Substances of the U.S. Environmental Protection Agency. The purpose of the study is to estimate the cost of performing certain tests for chemical toxicity and physical/chemical properties according to protocols developed by the Organization for Economic Cooperation and Development (OECD). The OECD tests considered in this study are those needed to provide the data included in the OECD Minimum Premarket Data set (MPD).

The MPD is a set of data designed to support premarket assessment of new chemicals in the twenty-four OECD member nations. In January, 1981, EPA published a Federal Register notice recommending that the MPD be developed by manufacturers of chemical substances subject to the new chemical notification program of the Toxic Substances Control Act (TSCA). This notice also recommended the use of test protocols from several sources, including the OECD. Both the development of the MPD and the use of the OECD protocols is voluntary. The cost data in this study, which represents the first attempt to estimate the cost of performing OECD tests in this country, are intended to help manufacturers make testing decisions.

The OECD test protocols are being made available through the Industry Assistance Office of the Office of Pesticides and Toxic Substances (800 424-9065).

This report was submitted in fulfillment of Task Order Number 4 of Contract Number 68-01-5864, by Enviro Control, Inc. Work was completed in January 1981.

The study is not an offical EPA publication. The accompanying cost estimates represent the views of the contractor who performed the study. It cannot be cited, referenced, or represented in any respect in any such proceedings as a statement of EPA's view regarding the cost of these protocols.

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COST ANALYSIS METHODOLOGY AND PROTOCOL ESTIMATES:

OECD Minimum Pre-Market Data Test Protocols

Introduction

The following methodology for estimating the cost of OECD (Organization for Economic Cooperation and Development) testing protocols has been designed to provide, as completely as possible, a representative estimate of testing costs in the United States. The methodology has been developed from contractor experience, review of previously published costing methods, and both formal and informal surveys of other testing laboratories, chemical and pharmaceutical companies, and prime contractors for Federal testing programs.

The cost estimating procedures are on a per chemical tested basis. The accuracy of cost estimates is directly proportional to the degree of detail specified in each protocol. If certain protocol details are not specified, then either assumptions must be made as to the intent of the test author(s), or broad ranges of component costs must be incorporated into the cost estimating procedure to encompass the entire range of protocol possiblities. These prices are for single tests only; the total cost of any testing battery will depend upon which of the tests are performed.

Even if all necessary details of a protocol are clearly specified, the estimated cost of conducting a study may vary greatly from laboratory to laboratory.

Cost estimate variance between testing laboratories originates from many sources, such as:[2,4,10,31]

- understanding of the nature of the chemical to be tested
- overhead rates
- salary rates
- in-house expertise
- use of outside consultants and subcontractors
- worker productivity and efficiency
- degree of automation
- acquisition of expendable supplies
- marketing strategies
- accuracy of protocol costing procedures

An understanding of the nature of the chemical to be tested may have a large effect on the time and cost estimated to conduct the study. Compound preparation and dosing times are both dependent upon the nature of the test article. Solid materials may be difficult to maintain in suspension, requiring a more detailed mixing regimen. Chemical characterisitics may dictate especially frequent sampling to assay for purity, stability, and concentration; and also dictate the method by which assays are conducted.

Overhead rates may be significantly different between testing laboratories due to numerous interacting factors. The number of years that a laboratory has been in operation may influence the overhead rate. Relatively new laboratories have a smaller work force (very few of which are supported on overhead), a large capital expenditure for new equipment, and a sizeable expenditure for marketing to generate new business. Well established laboratories usually support many more employees on overhead and spend less on marketing and new equipment.[11]

The range and variety of experimental capabilities offered by a laboratory may also affect the overhead percentage. If the testing laboratory is one of many operational units, such

as a testing laboratory associated with a large chemical manufacturing company, the overhead rate may be inordinately burdened by cost factors from other operational units, and is thus difficult to compute accurately.[2] The more varied the laboratory capabilities are, the more equipment and personnel are required for operation. The more limited the experimental capabilities, the more the laboratory must rely on expensive consultants and subcontractors to perform specialized technical tasks.

The efficiency of the work force is also a variable factor. Higher salary rates for productive, well-qualified personnel may balance against lower salaries paid to less efficient personnel requiring more training and exhibiting greater turnover. A high degree of automation may boost worker speed and efficiency, yet the cost of automation significantly increases the overhead rate; automatic watering systems reduce animal care time, but cause an increased capital expenditure. A similar situation occurs when computerized systems are introduced to collect, process, and store data, which reduces technician and report writer times.

All expendable supplies required to conduct a study (e.g., stock, cultures, experimental animals, chemical reagents, etc.) are subject to many factors which cause variations in acquisition costs. For example, market fluctuations and the availability and choice of supplier directly affect the price of expendable supplies. The proximity of the testing laboratory to the supplier will affect shipping costs. Laboratories conducting a high volume of studies are more likely to take advantage of volume discounts.

Marketing strategies employed by various laboratories may also significantly affect the costs of conducting different protocols. As in most businesses, the overall profit realized by a testing laboratory is proportional to the volume

of tests performed. In order to encourage volume testing, some laboratories will offer discounted prices for multiple testing packages which are significantly lower than the sum of the costs of the individual components tests. Low estimates may also be given to solicit new business when testing volume is low, or when a laboratory wishes to expand its testing capabilities into new areas.

The accuracy and experience of cost estimating personnel can also significantly affect estimated costs of specific protocols. Personnel with little experience may completely overlook certain cost components or under- or over-estimate other components. Some laboratories routinely conduct certain types of studies, while seldom or never conducting others, even though they have the necessary equipment and expertise. Cost estimates obtained for the routinely conducted tests will most likely be accurate, while estimates for other protocols may show marked variation from average or actual costs.

Recognizing all of the possible sources of cost variation, the proposed cost estimating methodology has been constructed by incorporating best estimates of industry average figures for all component costs, such as task times, salaries, overhead rates, supply costs, and profit margins. Industry averages were estimated by obtaining this confidential information from testing laboratories, federal prime contractors, manufacturing companies that contract similar studies, personnel placement firms, industry trade associations, and the contractor's own experience in the field. Despite this effort at designing an accurate cost estimating methodology, the final estimates generated are only considered to be representative of the prices that might actually be charged for conducting a study in the United States.

CHAPTER I

BASIC COST ESTIMATING PROCEDURES

I.A. Introduction

Cost estimates are calculated by separating each protocol into components and estimating the cost of each component. The major cost components are Direct Labor, Overhead, Other Direct Costs, General and Administrative Costs and Profit or Fee. These major areas are subdivided as described below, and estimated to arrive at a Best Estimate. The cost of most tests will fall into a range built around the Best Estimate.

In some cases, price quotations and/or cost component requirements were obtained from several commercial testing laboratories in lieu of best estimates. Laboratory surveys were relied upon when the contractor did not have direct experience with conducting the test.[26,28]

I.B. Costing Formula

The following components are estimated to provide a Best Estimate:

Direct Labor Cost

- task identification
- personnel requirements
- task time requirements
- personnel salary rates

Overhead Costs

Other Direct Costs

- expendable supplies

General and Administrative Costs

Profit or Fee

These component costs are combined in the following formula to calculate the Best Estimated Cost:

$$DL + OH + ODC + G\&A + F = \underline{\text{Best Estimate}}$$

where: DL = Direct Labor Cost
OH = Overhead, as a % of DL
ODC = Other Direct Costs
G&A = General and Administrative Costs, as a % of (DL + OH + ODC)
F = Fee, as a % of (DL + OH + ODC + G&A)

I.C. Direct Labor Cost

The estimation of direct labor cost involves four separate considerations:

1) Task Identification
2) Personnel Requirements
3) Task Time Requirements
4) Personnel Salary Rates

In addition, salary and inflation adjustment factors are applied if appropriate to account for wage increases likely to occur during the performance of the study due to inflation and merit increases.

1. Task Identification

Each protocol is evaluated by a scientist who is familiar with the particular type of study, and the specific tasks required to complete the study are identified.

2. Personnel Requirements

The types of professional and technical personnel required to complete each task are assigned to each respective task. The levels of education and experience required are either specified in the protocol, in federal regulatory requirements, or are established by general consensus and practice in the industry. Examples follow:

Study Director - Ph.D. in toxicology, pharmacology, or related fields, with a minimum of 4-5 years experience in toxicology testing. This individual is responsible for all the overall conduct of the study.

Veterinarian - D.V.M.; Board-certified or eligible for certification by the American College of Laboratory Animal Medicine with a minimum of two years of experience in laboratory animal medicine. This individual oversees all animal husbandry, veterinary care, and performs complete physical examinations.

Compound Preparation technician - B.S. degree in chemistry or other life science and a minimum of 1-3 years of experience in analytical or testing laboratories. This individual is responsible for the preparation of all test substances for dosing (e.g., dietary incorporation, dosing solutions, etc.).

Senior Technician - B. S. degree in life sciences, a minimum of 3 years experience in toxicity testing, and supervisory skills. This individual is responsible for the day-to-day operation of all technical aspects of the study during the in-life phase. Supervises Animal Technicians and Caretakers assigned to the study. Usually certified as an Animal Technician or Technologist by the American Association of Laboratory Animal Science (AALAS).

Aquatic or Fisheries Biologist - B.S. degree in Limnology, Ichthyology or other life sciences and a minimum of 1-3 years experience in testing laboratories. This individual is responsible for ascertaining the health status of all aquatic test animals and supervises technicians assigned to the study.

Microbiologist, Soil Scientist, Phycologist, Botanist- B. S. degree in microbiology, geology, phycology, botany or a closely related field as appropriate to the assigned area of responsibility and a minimum of 1-3 years of experience in testing laboratories. This individual performs or directly supervises all studies as related to the discipline involved.

Analytical Chemist - M. S. or B.S. degree in chemistry with 2-4 years of experience in environmental assays. This individual performs accurate chemical analyses of organic and inorganic compounds that may be found in biological systems and is responsible for instrumental techniques required in the analyses (i.e., gas, liquid chromatography, UV, IR, NMR, MS, and AA spectrometry).

Analyst - H. S. diploma or its equivalent and a minimum of one year of experience in laboratory testing plus a minimum of three months on-the-job experience in performing the measurements being considered.

Animal Technician - B. S. degree in life science or equivalent experience in animal testing laboratories. AALAS-certified or eligible for Animal Technician. Experienced in technical skills of dosing, observations, necropsy, and data collection.

Animal Caretaker - entry-level position. This individual is responsible for providing general animal care and husbandry services, including cage cleaning, feeding, and watering.

Clinical Laboratory Supervisor - B.S. degree in life sciences and a minimum of 3 years experience in clinical laboratory techniques. Certified as a Medical Technologist or Clinical Laboratory Technologist by HEW or the American Society of Clinical Pathology (ASCP). Oversees all hematology, clinical chemistry, and urinalysis assays.

Necropsy Supervisor - D.V.M. or equivalent certification or experience in laboratory animal surgery and necropsy. This individual oversees all necropsies and supervises necropsy technicians.

Necropsy Technician - A minimum of 1-2 years experience in animal testing laboratories and trained in necropsy and tissue trimming techniques.

Histology Supervisor - ASCP-certified Histotechnologist with a minimum of 3 years experience in histologic processing of tissues. This individual oversees all histology services and the production of slides for pathologic evaluation.

Histology Technician - certified or eligible for certification by the American Society of Clinical Pathology (ASCP) with a minimum of 1-2 years experience in histology techniques.

Veterinary Pathologist - Board-certified or Board-eligible doctoral-level pathologist with a minimum of 3 years of experience in veterinary pathology of laboratory animals. This individual supervises all scheduled necropsies and performs all microscopic examinations of tissues.

Report Writer Supervisor - B.S. in the life sciences with a minimum of 3 years experience in toxicological testing and technical writing. This individual oversees the production of all reports of toxicity studies.

Report Writer - B.S. in life sciences and at least one year experience in toxicological testing or report writing. This individual compiles, tabulates, and statistically analyzes test data and writes materials and methods and results under the supervision of professionals directing specific phases of the study.

Computer Programmer - B. S. in computer science or equivalent experience. This individual develops and operates all computer programs used for data collection, analyses, and tabulation.

Computer Coder - a minimum of one year experience in keypunching.

Report Typist - responsible for all technical typing involved in the production of final reports.

General Secretary - provides secretarial support to scientific and managerial personnel.

Quality Assurance Inspector - B. S. in life sciences and a minimum of 1-3 years experience in toxicological testing, quality control, and/or GLP compliance. This individual performs all inspections and audits necessary to insure that a study is performed in compliance with Good Laboratory Practice.

3. Task Time Requirements

The time to complete each identified task by the appropriate personnel is then calculated or estimated. During the course of a study, the time required to complete the tasks may change due to familiarity with routines and mortality of test animals. The estimates of task times used in this costing

methodology were obtained from published industry average figures, surveys of testing laboratories, and from contractor experience.[2,11,31]

4. Personnel Salary Rates

The hourly wage rates paid to each type of professional and technical personnel are then multiplied by the task times to arrive at labor dollars required to perform each task. The following wage and salary rates are estimates of current industry averages obtained from published figures, personnel placement firms, federal prime contractors, and testing laboratories:[1,11,31]

PERSONNEL	HOURLY WAGE	APPROXIMATE ANNUAL SALARY
Study Director	$17.80	$37,000
Veterinarian	14.00	29,000
Aquatic Biologist	6.70	14,000
Microbiologist	6.70	14,000
Soil Scientist	7.70	16,000
Phycologist	6.70	14,000
Botanist	6.70	14,000
Analytical Chemist	7.70	16,000
Analyst	4.00	8,400
Senior Technician	7.70	16,000
Animal Technician	6.00	12,500
Compound Prep. Technician	6.00	12,500
Animal Caretaker	4.00	8,400
Clinical Lab. Supervisor	10.00	21,000
Clinical Lab. Technician	6.00	12,500
Necropsy Supervisor	10.00	21,000
Necropsy Technician	5.00	10,400
Histology Supervisor	10.00	21,000
Histology Technician	6.00	12,500
Board-certified Pathologist	24.00	50,000
Board-eligible Pathologist	19.25	40,000
Report Writing Supervisor	10.00	21,000
Report Writer	6.00	12,500

Continued

PERSONNEL	HOURLY WAGE	APPROXIMATE ANNUAL SALARY
Computer Programmer	$ 8.50	$17,700
Computer Coder	5.00	10,400
Report Typist	5.00	10,400
General Secretary	6.00	12,500
Quality Assurance Inspector	10.00	21,000

Salary Adustment

Direct Labor Dollars are modified by a salary adjustment factor to account for inflationary and merit wage increases likely to occur during the performance of studies lasting longer than one month. The adjustment factor is calculated as follows:

$$\frac{\text{Duration of In-life phase (months)} \times 2}{\text{12 months/year}} \times 8\% \text{ wage increase per year}$$

The in-life phase is multiplied by 2 because personnel work on a project until the final report is issued. As a rule of thumb, the duration of the post mortem phase of the study is estimated to be as long as the in-life phase.[31]

I.D. Overhead

The overhead rate is applied as a percentage of the total direct labor cost. This percentage represents a broad spectrum of costs incurred in varying degrees by all laboratories performing tests. The cost of maintaining the laboratory facility, i.e., rental or mortgage, communication services, utilities, depreciation and amortization of non-expendable equipment, insurance, property taxes, repairs, and maintenance are included in overhead. Cost incurred as direct support are included, i.e., recruitment and relocation of personnel, fees and licenses, printing and reproduction, publications, office supplies and materials, postage and delivery, travel and computer expenses.

Fringe benefits are also included in overhead costs. These benefits may include administrative, sick, and annual leave; holiday remuneration; group insurance plans (hospitalization, life, disability); pension plans; workman's compensation; unemployment and F.I.C.A. taxes; and tuition reimbursement. The cost of fringe benefits may vary considerably based on the number of employees receiving benefits

and the range of benefits offered.[4]

Finally, overhead encompasses indirect labor costs, i.e., security and supervisory labor. Indirect labor provided to perform support functions, such as standard operating procedures development, protocol evaluation, and editing of reports, are included in overhead.

Overhead rates are difficult to obtain from company personnel due to the confidential nature of financial information. However, prime contractors for federal testing programs have access to overhead rates, and private contacts within testing laboratories sometimes provide estimates. The rates vary considerably, from 50% to 250% of direct labor costs. Taking into consideration the recent dramatic rise in the cost of energy and the effects of GLP compliance, an overhead rate of 115% is used in this cost estimating method as an accurate estimate of the industry average.

I.E. Other Direct Costs

Other direct costs consist of 1) overtime premium, 2) consultant or subcontracted services and 3) expendable supplies required to complete the test protocol.

1. Overtime Premium. To comply with test protocols, designated employees may be required to complete tasks requiring more time than standard working hours provide. When the task specified by the test standard protocol require labor beyond eight hours per day or 40 hours per week, compensating salary may be provided at one and one-half times the normal hourly rate.

2. Consultant or Subcontracted Services. Since few laboratories are equipped to perform all tests required or services dictated by the broad range of test protocols, laboratories may enlist the aid of professional consultants or subcontract with other laboratories for specific services. These fees are included in other direct costs. Examples may include specialized analytical procedures, or veterinary ophthalmologist services.

3. Expendable Supplies. Expendable supplies represent those items ordered and used specifically for the test protocol. Each protocol is evaluated by an experienced scientist in order to estimate the dollar amount of expendable supplies likely to be utilized in conducting the test standard protocol. This figure does not include the cost of any major instruments which could be used in the testing of many different chemicals.[11] Only expendables such as experimental animals, reagents, disposable supplies, and items used specifically for the test in question are included. For example, to conduct a partition coefficient assay, a centrifuge is required. The cost of the centrifuge itself is not included in other direct costs (although the depreciation and amortization of this equipment is reflected in overhead costs), but the reagents necessary to prepare the sample for centrifugation and any disposable centrifuge tubes and caps are considered as other direct costs.

Inflation Adjustment - the sum total of all Other Direct Costs is modified by an inflation factor to account for increases in the cost of supplies during the course of the study. This factor is calculated as follows:

$$\frac{\text{Duration of In-Life Phase (months)}}{\text{12 months per year}} \times \text{10\% inflation per year}$$

I.F. General and Administrative Cost

These cost represent the salaries of administrative and support personnel not actually engaged in the study, but whose labor is necessary to the operation of the laboratory. Examples of such functions include management, personnel, purchasing, accounting, marketing, legal counsel, and bid and proposal staff.[31]

As with overhead rates, G & A rates are difficult to obtain from private companies. However, estimates of G & A range from [illegible] to 25% of the sum of direct labor, overhead, and other direct costs. An estimated average of 10% is utilized in this costing methodology.[4]

I.G. Profit or Fee

This figure represents the profit margin applied to the actual cost of performing a study. Due to the confidential nature of this type of information, it is difficult to obtain an accurate survey of profit percentages. The range may be from 8% to 35%. An estimated average of 20% is used in this costing methodology.

CHAPTER II

PHYSICAL CHEMICAL PROPERTIES

II.A. Introduction

Through an understanding of the physical and chemical properties of chemical compounds, a better understanding of the potential risk presented to man and environment can be obtained. The method of release to the environment and therefore the route of human exposure can be better understood by learning the water solubility, density, particle size distribution, etc. of chemical compounds. An indication of the mobility inherent in chemical compounds released in the environment can be ascertained by investigating the vapor pressure, adsorption/desorption, etc. of chemical compounds. Physical and chemical parameters serve also to indicate further testing necessary for a complete profile of the risk associated with chemical compounds.[22]

Variation may result in the reported cost of these tests if a number of samples are submitted for analysis at the same time. Discounts are offered by some laboratories based on the number of samples to be analyzed. A combination of tests may also cause a reduction in cost. For example, using the photocell detection method for boiling point/boiling range determination also allows for measurement of melting point/melting range. Also, the dynamic method of determining boiling point/boiling range also allows for measurement of vapor pressure. Variation in the cost of physical chemical properties testing may be as much as 2 fold.

II.B. Melting Point/Melting Range

The melting point/melting range reflects the temperature at which a chemical compound changes in physical state from solid to liquid. Several different methods may be

employed for this determination, including photocell detection, melting microscope, meniscus method and freezing point methods. The best estimate for this test is $100. Variance will occur based on the method utilized. The method to be selected will be determined by the nature of the chemical compound. Compounds that have high melting points will require more time and difficulty to test. Compounds that decompose, show extended softening, react or volatilize may require more specialized methods and will entail more cost for analysis.

II.C. Boiling Point/Boiling Range

The boiling point/boiling range reflects the temperature at which a chemical compound reaches boiling temperature. This property indicates the physical state at which a chemical compound will exist in the environment. Several different methods may be employed for this determination including the dynamic method, distillation method and photocell detection method. The best estimate for this test is $50. Variance will occur based on the method utilized. The method to be selected will be determined by the nature of the chemical compound. Liquids that undergo chemical reaction below the boiling point, such as oxidation, rearrangement, or degradation and compounds containing impurities may require more specialized methods and, therefore, higher costs.

II.D. Density of Liquids and Solids

The density of a chemical compound is a measurement of the mass of a unit volume of the compound. This property may assist in making predictions about the distribution and settling potential of the compound. Several different methods may be employed for this determination, which will be directly dependent on the physical nature of the compound.

The determination of the density of solids

may be determined by pycnometer, air comparison, pycnometer or hydrostatic balance. Solids can rise in water or sink as deposits, becoming incorporated into silt or soil. They can also enter the atmosphere as particulate dust, which may later settle as a soil contaminant.

The density of liquids may be determined by hydrometer, hydrostatic balance, immersed ball, pycnometer, or oscillating density meter methods. Determination of liquids is dependent on viscosity, solubility and interfacial tension, which also effect the distribution of liquids within the environment.

The density of gases may be calculated on the basis of molecular formula or weight using the gas law. Gases will settle or become dispersed depending on their density and also on their diffusion patterns with other molecules and air turbulence conditions. Since calculation is the usual method of determining gaseous density, it is not included in the estimate to follow.

The best estimate for density determinations in solids and liquids is $50. Variance will occur based on the method utilized.

II.E. Vapor Pressure

The vapor pressure of a chemical compound is a measurement of the pressure at which a compound is in equilibrium between rate of vaporation and condensation. It is, therefore, an indication of the volatility of a compound, which provides an understanding of the partitioning behavior of a compound. Several different methods may be employed for this determination including the dynamic, static, isoteniscopic, vapor pressure balance and gas saturation methods. The best estimate for this test is $300. Variation will occur based on the method utilized and the chemical nature of the compound. Compounds with

low vapor pressure may sometimes require long sampling times and, therefore, additional cost.

II.F. Water Solubility

The water solubility of a compound is a measure of the mass concentration required for saturation in water. This property indicates the mobility of the chemical compound within the environment and serves as a prerequisite for other tests which will be used for risk assessment. Two different methods may be utilized, depending on the chemical nature of the compound. Compounds with low solubilities can be tested with the column elution method. Compounds with higher solubilities may be determined with the flask method. The best estimate for this test is $250. Variance in price will occur based on the nature of the chemical compound. Determinations for compounds with low solubilities may be more costly than those for compounds with high solubilities.

II.G. Partition Coefficient, n-octanol/water

The partition coefficient reflects the equilibrium concentration ratio of an organic chemical compound as it partitions between a lipophilic solvent (n-octanol) and water. This property indicates the probable mobility of chemical compound between water and living organisms. It also serves as a prerequisite for bioaccumulation determinations since n-octanol simulates fat and will indicate the storage and ecological magnification potential of organic chemicals in the fats of living organisms. The shake flask method is employed. The two phases are thoroughly mixed with the compound and allowed to equilibrate. Both phases are analyzed for compound content. The best estimate for this test is $250. Variance will occur based on the chemical nature of the compound to be tested. Surfactants take much more time to equilibrate. The formation of emulsions causes problems in reaching equilibrium.

Metal-organic compounds cannot be assayed with this test, so other methods must be selected. The chemical analysis techniques selected to assay the n-octanol and water partitions will be dictated by the nature of the chemical compound to be assayed. This factor may cause great variation in cost.

II.H. Hydrolysis (as a function of pH)

Hydrolysis is a measurement of the reaction potential of a chemical with water. The reaction potential is determined as a function of time until a minimum of 90% of the reaction has occurred. This property is an indication of one degradative pathway a chemical compound will follow and the potential byproducts that will be produced in the environment. The hydrolysis is allowed to take place at four different pH levels and then the solution is analyzed to determine the per cent reduction in the initial concentration and the reaction rate constant is calculated. The best estimate for this test is $250. Variance will occur based on the analytical method employed for analysis, which is directly dependent on the compound to be tested. Unstable compounds may require specialized methods and could, therefore, entail additional cost.

II.I. Spectra (UV and Visible)

The absorption spectrum of a chemical compound reflects the particular chemical form of the compound. This property indicates the potential of a chemical compound to undergo photochemical degradation and gives an indication of the byproducts that may be produced within the environment. The best estimate for this test is $200. This test does not vary from chemical to chemical substantially, so most costs encountered should fall within a close range.

II.J. Adsorption/Desorption to Soil Types

The adsorption/desorption potential of a chemical compound is a measure of the decrease in concentration that results when aqueous solutions of the compound are in contact with different soil types. This property indicates the potential mobility of the chemical compound within the soil environment. Three soil types that vary in content and exchange capacity are utilized. The best estimate for this test is $2,000. Variability in cost may result based on the sorption behavior of the compound. Preliminary screening tests of the nature described may not be comprehensive enough for adequate determination. Secondary steps may be required entailing higher costs. Analytical assay of the compound solution may also be a source of variation in cost. The analytical method will be dictated by the nature of the chemical compound.

II.K. Dissociation Constant

The dissociation constant is a measure of the tendency of a compound to split into two or more ions. This property indicates the chemical state or states in which a compound will exist in the environment. Several different methods may be employed for this determination including the titration

method, the spectrophotometric method and conductometric method. The best estimate for this test is $150. Variance will occur based on the method utilized. The method to be selected will be determined by the nature of the chemical compound. Solubility of the chemical compound will be a determining factor. The presence of emulsions may require specialized methods. The analytical methods utilized will also be determined by the nature of the chemical compound and may have a great effect on cost.

II.L. Particle Size Distribution

The particle size distribution of a chemical compound is a measure of the size and radius distribution of water insoluble particles and fibers that characterize the compound This property impacts on the mobility of a chemical compound in water and air and identifies the potential health hazard that may arise from inhalation and ingestion of particles and fibers. Two different methods may be employed. The effective hydronamic radius determination may be used for particulate compounds that do not form fibers. The best estimate for this test is $100. If fibers do form,microscopic examination with scanning or transmission electron microscopy is required for determination. These methods are more costly, and will increase the best estimated cost. Variability in cost will also arise based on the chemical nature of the compound. The occurrence of fiber breakage, clumping or sample contamination may require more specialized methods and entail additional cost.

II.M. Summary

The following is a summary of best estimates for physical/chemical property tests. The estimates listed are for single tests only. Estimates are not additive, as a chemical compound may be evaluated using one test, a group of tests, or none of the tests listed, based on the nature

of the chemical and its intended use.

Protocol	Best Estimate
Melting Point	$ 100
Boiling Point	$ 50
Density	$ 50
Vapor Pressure	$ 300
Water Solubility	$ 250
Partition Coefficient	$ 250
Hydrolysis	$ 250
Spectra	$ 200
Absorption/Desorption	$2000
Dissociation Constant	$ 150
Particle Size Distribution	$ 100

CHAPTER III

ECOTOXICOLOGY

III.A. Introduction

Ecotoxicological investigations provide data necessary to understand the potential risk a chemical compound poses as it interacts within ecosystems. Biota representative of populations and communities within an ecosystem are exposed to the test compound. This exposure is designed to represent the actual environmental exposure that will be encountered by organisms existing in the ecosystem, i.e. in water, soil or air. The test compound will undergo degradation volatilization, and adsorption as it would within the environment. Manifestation of toxic effects such as death, reproductive inhibition, life cycle effects, alteration in growth, and behavioral changes can be identified. Indications of broader changes in species diversity or dominance, can be given.

Single species ecotoxicity tests provide necessary preliminary data. Three single species ecotoxicity tests are presented as requirements for assessing the effects of a chemical compound on ecosystems. These tests are a Fish LC_{50}, a Daphnia LC_{50} and an Algal IC_{50}. Data from these preliminary tests will serve as indicators for further testing so that a complete profile of the risk produced within ecosystems can be ascertained.[6,8,23,29,30] The variation in cost for these tests will be minimal, and will arise mainly from the analytical assay techniques utilized.

III.B. Acute Toxicity LC_{50}, Fish (96 hour, Static)

This test provides data for determination of the median lethal concentration (LC_{50}) of a chemical compound in the test species. This preliminary determination helps to assess the potential risk of the compound when compared to other known chemical compounds.

A range finding test is performed if the toxicity of the test compound is not already known. This preliminary (RF) test establishes the range of test substance concentrations to be used in the LC_{50} determination. The best estimate for the range finding test is $150. The best estimate for the LC_{50} is $400.

Additional costs will result from these tests based on the analytical assay techniques employed. Due to the nature of chemical compounds, different methods will be used and costs will vary. The approximate cost for analytical assay is $50/sample. Assuming two samples will be required for the range finding study and 12 samples (two replicates of six chambers) will be required for the LC_{50}, the total best estimate for analytical determination is $700.

The chemical nature of the compound may also dictate other cost variables. If mortality continues beyond 96 hours, the duration of the test may be extended for adequate determination of the LC_{50}, entailing additional cost. Flow through or static renewal methods may also be utilized, depending on the nature of the chemical compound. These methods may entail additional cost. The best estimate for a Fish LC_{50} (static) determination is $1250 (RF plus analytical).

III.C. Reproduction Study And LC_{50}, *Daphnia magna* (14 days)

This test also allows for determination of LC_{50}, and also allows for an assessment of reproductive effects since the test organisms are exposed for more than a complete generation cycle (three broods).

A range finding test is performed if the toxicity of the test compound is not already known. This preliminary test establishes the range of test substance concentrations to be used in further tests. The best estimate for the range finding test is $100. The best estimate for the reproduction study is $600.

Additional costs will result from these tests based on the analytical assay techniques employed. Due to the nature of chemical compounds, different methods will be used and costs will vary. The approximate cost for analytical assay is $50/sample. Assuming two samples will be required for the range finding study and 12 samples (two replicates of six chambers) will be required for the reproduction test, the total best estimate for analytical determination is $700.

Combining the range finding test ($100), the reproduction test ($600) and the analytical assay ($700) yields a total best estimate of $1400.

III.D. Growth Inhibition Study, Unicellular Alga (4 days)

This test provides data for determination of the median inhibitory concentration (IC_{50}) of a chemical compound with respect to the test species. This preliminary determination helps to assess the potential risk presented by a compound to primary producers in the environment.

A range finding test is performed if the toxicity of the test compound is not already known. This preliminary test establishes the range of test substance concentrations to be used in the IC_{50} determinations. The best estimate for the range finding test is $150. The best estimate for the IC_{50} is $600.

Additional costs will result from these tests if analytical assay techniques are employed. The test protocol does not require assay and most laboratories contacted do not conduct analysis. Due to the nature of chemical compounds, different methods will be used if analysis is conducted and costs will vary. The approximate cost for analytical assay is $50/sample. Assuming two samples will be required for the range finding study and 12 samples (two replicates of six chambers) will be required for the IC_{50}, the total

best estimate for analytical determination is $700.

The chemical nature of the compound may also dictate another cost variables. The water solubility of the compound will have an influence on the method utilized and may cause some variation in cost.

The best estimate for Algal IC_{50} determination ($600) including range finding ($150) and analytical assay ($700) is $1450.

III.E. Summary

The following is a summary of best estimates for ecotoxicity testing. The estimates listed are for single tests only. The total estimates are not additive, as a chemical compound may be evaluated using one test, a group of tests or none of the tests listed based on the nature of the chemical and its intended use.

PROTOCOL[23]	BEST ESTIMATE	TOTAL ESTIMATE
Acute Toxicity LC_{50} (Fish)		$1250
Range Finder	$150	
LC_{50}	400	
Analytical Assay	700	
Reproduction Study (Daphnia)		$1400
Range Finder	$100	
Reproduction test	600	
Analytical Assay	700	
Growth Inhibition (Algae)		$1450
Range Finder	$150	
IC_{50}	600	
Analytical Assay	700	
Without Analytical Assay		($ 750)

CHAPTER IV

BIODEGRADATION/ACCUMULATION

IV.A. Introduction

Measuring the biodegradation and bioaccumulation potential of chemicals is important for assessment of the hazard presented by chemicals entering the environment. Five different tests are presented as options for the assessment of ready biodegradability, and two options are presented for the assessment of bioaccumulation. Selection of the appropriate test in each area will depend on the chemical nature of the compound to be tested and the means by which it will enter the environment.[21] Variation in the cost of these tests will be minimal, and will arise mainly from adjustments to methods dictated by the company.

IV.B. Ready Biodegradability

IV.B.1. Closed Bottle Test (Fischer Test)

This test measures biodegradability based on analysis of oxygen content. The chemical compound to be tested is dissolved in an inorganic medium, into which a mixed population of microorganisms is inoculated. A period of incubation follows in closed bottles placed in the dark in a constant temperature bath. Oxygen analysis over a 28 day period provides an indication of the degradation occurring. The best estimate for this test is $250. Variability in cost may result if the compound is difficult to solubilize into the inorganic medium. Special procedures to adjust for insolubility will cause an increase in cost.

IV.B.2. Biodegradability (Microorganisms - MITI Test)

This test measures biodegradability based on biochemical oxygen demand. The chemical compounds to be tested are solubilized into deionized water, or culture medium with activated sludge added. Microorganisms are added. Biochemical oxygen demand is measured continuously

as a means of measuring biodegradability, along with supplemental chemical analyses. The best estimate for this test is $9,000. Variability will again result based on the degree of difficulty presented by solubilizing the test compound. Volatile compounds require more specialized, more costly methods.

IV.B.3. Biodegradability (AFNOR Test)

This test measures biodegradability based on dissolved organic carbon analysis. The chemical compounds to be tested are dissolved in water and inoculated with chemiorganotrophic microorganism. Organic carbon remaining in solution is measured at several time intervals concluding with 42 days. The corresponding level of biodegradation is calculated. The best estimate for this test is $1,000.00. Variance in cost may be present based on the solubility of the compound. Methods may require adjustment for volatile compounds. Concentration of test compounds which inhibit the growth of microorganisms utilized may also require adjustments in method, causing additional cost variation.

IV.B.4. Biodegradability (Sturm test)

This test measures biodegradability based on CO_2 evolution. The chemical compound to be tested is added to liquid culture medium and inoculated with sewage microorganisms. The total amount of CO_2 evolved from the test system is measured. Biodegradation is calculated from this result. The best estimate of this test is $1,700. Variability in cost may be present based on the solubility of the compound. Insoluble compounds may be utilized as fine particles in suspension. Modifications to the compound concentration may be required if the test compound inhibits the growth of microorganisms utilized. These method adjustments may cause variation in cost.

IV.B.5. Screening Test With DOC Analysis

This test measures biodegradability based on dissolved organic carbon. The chemical compound to be tested

is dissolved in an inorganic medium and inoculated with a mixed population of microorganisms. Dissolved organic carbon is measured over a 28 day period. Biodegradation is measured as %DOC removed from the test system. The best estimate for this test is $700. Variability will result based on the solubility of the test compound. Modifications to the compound concentration may be required if the test compound inhibits the growth of microorganisms utilized. These method adjustments may cause variation in cost.

IV.C. Bioaccumulation

IV.C.1. Bioconcentration (Marine Organisms)

This test measures uptake of the test compound in mussels. An initial concentration of test substance is administered to mussels in marine aquaria. The system is allowed to equilibrate then terminated. Accumulation within the mussels is determined along with remaining, steady state concentration within the water. The best estimate for this test is $850. Variability will result based on the solubility of the test compound in sea water.

IV.C.2. Static Bioaccumulation in Fish

This test measures uptake of the test compound in fish. The test substance is administered to fish in fresh water aquaria and allowed to equilibrate for 8 days. Water is analyzed for the test compound during the test and upon termination. At termination the fish are also analyzed for accumulation of compound. The best estimate for this test is $2,000. Variance will result based on the nature of the chemical to be tested. Compound solubility, volatility, degradability, and polarity will cause this variability. These factors will determine

the method of chemical analysis to be used which can fluctuate greatly in cost.

IV.D. Summary

The estimates for the various options to be considered available for measuring under the requirement for Ready Biodegradability are as follows: Closed Bottle Test (Fischer) - $250, Biodegradability (Microorganisms) - $9,000, Biodegradability - $1,000, Biodegradability (Sturm test) - $1,700, and Screening Test With DOC Analysis - $700, making the range of cost for Ready Biodegradability $250 - $9,000, depending on which test is selected.

The best estimate for the options to be considered for measuring Bioaccumulation are as follows: Bioaccumulation (Marine Organisms) - $850, Static Bioaccumulation in Fish - $2,000, making the range of cost for Bioaccumulation $850 - $2,000, depending on which test is selected.

CHAPTER V

TOXICITY STUDIES FOR HUMAN HEALTH EFFECTS

V.A. Introduction

Assessments of physical and chemical properties, ecotoxicology, and potential for biodegradation and bioaccumulation provide indications of potential hazard presented by chemical compounds. Toxicity studies as described herein provide indications of the potential hazard that chemicals may present to human health. Relatively short term tests are used to provide a preliminary hazard assessment. The results may also indicate the need for further studies necessary to characterize the toxicity and aid in decisions as to further development of new chemical products.

The tests are designed to examine the relationship between dose and adverse effects demonstrated, and where possible, to develop information on the physiological mode or mechanism of toxic effect.[9]

The different tests included are designed to take into account the possible routes of human exposure (oral, dermal, inhalation) and the possible modes of toxic effect (from organ system effects to chromosomal aberration). Since such a variety of effects are possible, flexibility in experimental design must be present to allow for adequate detection. Where flexibility exists, variation in cost is produced. Variation in test procedures will cause variance in the estimated cost of conducting a study from laboratory to laboratory. This variation may be as much as 10 fold.

V.B. Acute Toxicity[12,24,27,30]

V.B.1. Acute Oral Toxicity[13]

Acute oral toxicity is measured by administering a single exposure of the chemical compound by gavage in graduated doses to multiple groups of experimental animals, with an observation period of at least 14 days. Toxic

effects are detected by observation during life and necropsy after death. The LD_{50} is statistically determined and used as a comparison index. Acute oral toxicity is an initial step in health hazard assessment. The best estimate for this test is $2,000. Variance will occur based on the species and strain selected for experimentation, on the duration of toxic effect, and on the extent of pathology conducted.

V.B.2. Acute Dermal Toxicity[14]

Acute dermal toxicity is measured by administering a single exposure of the chemical compound directly to the skin in graduated doses to multiple groups of experimental animals, with an observation period of at least 14 days. Toxic effects are detected by observation during life and necropsy after death. The LD_{50} is statistically determined and used as a comparison index. Acute dermal toxicity is used as a basis to determine potential health hazard from dermal exposure and may also provide information on dermal absorption potential and mode of toxic action. The best estimate for this test is $2,800. This estimate is made with the assumption that rabbits are the species utilized, and that dosing is to nonabraded skin using semi-occlusive dressings. Variance will occur when other species are utilized, when the method of skin application is different and on the extent of pathology conducted.

V.B.3. Acute Inhalation Toxicity[15]

Acute Inhalation Toxicity is measured by administering a single, defined period exposure (usually 4 hours) of the chemical compound directly in graduated doses to multiple groups of experimental animals, with an observation period of at least 14 days. Toxic effects are detected by observation during life and necropsy after death. The LC_{50}, median lethal concentration, is statistically determined and used as a comparative index. Acute inhalation toxicity is used as a basis to determine potential health hazard from the inhalation of volatile, aerosol or suspended particulate substances. The best estimate for this test is $3,300.

Variance will occur based on the species and strain selected for the test, the extent of toxicant delivery checks, the analytical method used for determination and the extent of pathology performed.

V.B.4 Acute Dermal Irritation/Corrosion[16]

Acute dermal irritation or corrosion is measured by administering a single dose of the chemical compound directly to the skin of experimental animals. Toxic effects are observed and scored for magnitude. Acute dermal irritation or corrosion is used as a basis to determine the possible hazard arising from exposure of the skin to chemical compounds. The best estimate for this test is $700. Variation may result based on the species and strain selected and on the extent of toxicity produced.

V.B.5 Acute Eye Irritation/Corrosion[17]

Acute eye irritation or corrosion is measured by administering a single dose of the chemical compound directly to the eyes of experimental animals. Toxic effects are observed and scored for magnitude. Acute eye irritation or corrosion is used as a basis to determine the possible hazard arising from exposure of the skin to chemical compounds. The best estimate for this test is $450. Variation may result based on the species and strain selected and on the extent of toxicity produced.

V.B.6 Skin Sensitization[18]

Skin sensitization is measured by exposing experimental animals to a chemical compound, then administering another challenge exposure after a period of time. Resultant hypersensitive induction can be detected in this manner. Skin sensitization is used as a basis to determine the potential hazard for sensitization produced by repeated exposure to chemical compounds. The best estimate for this test is variable based on the method employed:

METHOD	BEST ESTIMATE
Draize Test	$ 6,700
Freund's Complete Adjuvant (FCAT)	3,900
Guinea Pig Maximation Test	5,500
Split Adjuvant Technique	3,200
Buehler Test	3,500
Open Epicutaneous Test	3,200
Mauer Optimization Test	3,850

V.C. Repeated Dose Toxicity[19,20]

Repeated dose toxicity is measured by administering repeated doses of a chemical compound by the probable route of human exposure, in graduated doses to multiple groups of experimental animals, for a period of 14 to 28 days. Toxic effects are detected by clinical observation and by clinical laboratory determinations, necropsy, and histopathologic assessment. The results provide information to indicate the potential hazard produced by repeated exposures to a chemical compound. The best estimate for this test, based on oral exposure by gavage, is: 14 day exposure, $10,200; 28 day exposure, $12,800. Variation will occur based on the species and strain selected for experimentation, the extent of clinical laboratory determinations, and the extent of histopathologic assessment performed.

V.D. Mutagenicity

V.D.1 Reverse Mutation Assay (*S. typhimurium*)

The reverse mutation assay in *Salmonella typhimurium* is a measure of gene mutation produced by chemical compounds in a histidine requiring strain. Revertant, histidine independent strains of *S. typhimurium* are produced by point mutations. The number of revertant colonies in five strains are compared to spontaneous revertants in a control system to detect the presence of increased mutation produced by the chemical compound. Reverse mutation assay is used as a basis to determine potential human mutagenic agents at the gene level. The best estimate for this test is $1,000. Variability will occur based on the number of replicates performed.

V.D.2 Reverse Mutation Assay (*E. coli* WP_2)

The reverse mutation assay in *Escherichia coli* WP_2 is a measure of gene mutation produced by a chemical compound in a tryptophane requiring strain. Revertant tryptophane independent strains of *E. coli* WP_2 are produced by point mutations. The number of revertant colonies in three strains are compared to spontaneous revertants in a control system to detect the presence of increased mutations produced by the chemical compound. Reverse mutation assay is used as a basis to determine the potential for mutagenicity and carcinogenicity. The best estimate for this test is $350. Variability will occur based on the number of strains utilized and the number of replicates performed.

V.D.3 *In Vitro* Mammalian Cytogenetics

The *in vitro* cytogenetics test is a measure of chromosomal aberrations produced in cultured mammalian cells exposed to chemical compounds. The exposed cell cultures are treated with a spindle inhibitor, e.g. cholchicine, to arrest cells in metaphase. The cells are stained and examined for structural and numerical aberrations. Structural changes resulting from breakage and reunion in chromosomes and chromatids as well as numerical changes resulting in aneuploidy and polyploidy can be detected. The *in vitro* cytogenetics test is used as a basis to determine potential mutagenicity at the chromosome level. The best estimate for this test is $3,000. Variability will occur based on the cell line used for the detection and the method employed.

V.D.4 *In Vivo* Mammalian Bone Marrow Cytogenetics

The *in vivo* cytogenetics test is a measure of chromosomal aberration produced in the bone marrow cells of animals exposed to chemical compounds. The harvested bone marrow cells of exposed animals are treated with colchicine, a spindle inhibitor, to arrest cells in metaphase. The cells are stained and examined for structural and numerical aberrations. Structural changes resulting from breakage and reunion in chromosomes and chromatids as well as numerical changes resulting in aneuploidy and poly-

ploidy can be detected. The *in vivo* cytogenetics test is used as a basis to determine potential mutagenicity at the chromosome level. The best estimate for this test is $13,000. Variability will occur based on the species and strain utilized for the detection and the method employed.

V.D. 5 Micronucleus Test

The micronucleus test is a measure of chromosomal aberration produced in the bone marrow cells of animals exposed to chemical compounds. The harvested bone marrow cells of exposed animals are stained and scored for the presence of acentric fragments or chromosomes that lag behind during the anaphase stage of cell division, or micronuclei. Polychromatic erythrocytes are the cells utilized since they lack a nucleus facilitating the detection of micronuclei. Since micronuclei occur naturally, the quantity of micronuclei associated with increasing levels of test compound is compared with positive and negative controls for assessment. The micronucleus test is used to determine human mutagenic agents at the chromosome level. The best estimate for this test is $2,000. Variability will occur based on the species and strain utilized for the determination and the method utilized.

V. E. Summary

The following is a summary of best estimates for toxicity studies performed to investigate human health effects. The estimates listed are for single tests only. Estimates are not additive, as a chemical compound may be evaluated using one test, a group of tests, or none of the tests listed, based on the nature of the compound and its intended use.

V.E. Summary (con't)

PROTOCOL	BEST ESTIMATE
Acute Oral Toxicity	$ 2,000
Acute Dermal Toxicity	2,800
Acute Inhalation Toxicity	3,300
Acute Dermal Irritation/Corrosion	700
Acute Eye Irritation/Corrosion	450
Skin Sensitization:	
Draize Test	6,700
FCAT	3,900
Guinea Pig Maximization Test	5,500
Split Adjuvant Test	3,200
Buehler Test	3,500
Open Epicutaneous Test	3,200
Mauer Optimization Test	3,850
Repeated Dose Toxicity (oral gavage)	
14 Day Exposure	10,200
28 Day Exposure	12,800
Reverse Mutation Assay *(S. typhimurium)*	1,000
Reverse Mutation Assay *(E.coli* WP_2)	350
In Vitro Mammalian Cytogenetics	3,000
In Vivo Mammalian Bone Marrow Cytogenetics	13,000
Micronucleus Test	2,000

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50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO. EPA-560/4-81-002	2.	3. Recipient's Accession No.

4. Title and Subtitle
Cost Analysis Methodology and Protocol Estimates: OECD Minimum Pre-Market Data Test Protocols

5. Report Date
6. January, 1981

7. Author(s) Janis C. Kurtz, Alan Cohen

8. Performing Organization Rept. No.

9. Performing Organization Name and Address
Enviro-Control, Inc.
Borriston Laboratories, Inc.
11300 Rockville Pike
Rockville, Maryland 20852

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C) 68-01-5864
(G)

12. Sponsoring Organization Name and Address
U.S. Environmental Protection Agency
OTS/ETD/RIB (TS-779)
401 M Street, S.W.
Washington, D.C. 20460

13. Type of Report & Period Covered
Cost Document for Recommended Guidelines

14.

15. Supplementary Notes

Project Officers: Joye Akridge and Sammy K. Ng

16. Abstract (Limit: 200 words)

The purpose of this study is to estimate the cost of the protocols for the Organization for Economic Cooperation and Development (OECD) Minimum Premarket Data (MPD). OECD is an international organization of 24 member nations whose membership includes the major chemical producers of the non-communist world. The MPD is designed for premarket assessment of the new chemicals in the OECD member nations. The base set of premarketing data which EPA is recommending is identical to the MPD developed by the OECD. The protocols were costed by first breaking them down into the various cost components and then costing each component seperately. The contractor's knowledge plus limited outside knowledge from other test labs was used in determining the cost figures.

17. Document Analysis a. Descriptors

Cost Analysis for OECD Minimum Pre-Market Data Test Protocol

b. Identifiers/Open-Ended Terms

OECD Base Set
Economic Analysis
Premanufacture Test Guidelines

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report) non-sensitive	21. No. of Pages
	20. Security Class (This Page) non-sensitive	22. Price

(See ANSI-Z39.18) See Instructions on Reverse OPTIONAL FORM 272 (4-77) (Formerly NTIS-35) Department of Commerce

*U.S. GOVERNMENT PRINTING OFFICE: 1981 341-082/232 1-3

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