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Biomedical Data Validation Through an On-Line Computer System

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BIOMEDICAL DATA VALIDATION THROUGH AN ON-LINE COMPUTER SYSTEM

by

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

This paper presents how quality assurance controls were included within the computer programming for a short term test -- the Salmonella suspension assay for mutagenesis.

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INTRODUCTION

Within the biomedical disciplines there are a variety of testing procedures used routinely within many separate laboratories. Since health, research and regulatory decisions are being based upon the results from many laboratories, there is a basic need for assuring the quality of the data. In the area of microbial mutagenesis, the use of Salmonella typhimurium as an indicator organism for mutational events is employed by many laboratories across the country. The various procedures available are rapid, relatively simple, sensitive and are used in a variety of laboratory situations including private industry, government and university laboratories. Presently, a great deal of emphasis is placed upon these types of tests as prescreens for substances that may be human mutagens and potential carcinogens. Therefore, the use of a system involving Salmonella typhimurium could provide an excellent pilot study for methods involved in data validation. Data validation is used in this context to mean the process by which generated data is filtered and accepted or rejected by objective criteria. Likewise, computerization provides a potential means for systematically applying a predetermined set of objective criteria in a rapid non-biased manner. With the use of TSO (Time Sharing Option), portions of the data validation can be conducted during the performance of a biological test. This article will describe the design of a pilot system for the on-line computer assistance of testing protocols and data validation. The scientific protocols and initial computerization have been completed and the system will be tested in a laboratory situation in the near future by the National Institute of Environmental Health Sciences.

DESCRIPTION OF TEST:

From a variety of microbial mutation test systems, the suspension test using a mammalian activation system was chosen because it is well defined and is a quantitative test system.[1] The more commonly used Ames plate incorporation method is only semiquantitative. We also chose to compare three strains of Salmonella typhimurium and a forward mutation strain of K-12 E. coli.[2] In simple terms, the test involves the combining of the bacterial strain with a compound and a mammalian activation system into an Erlenmeyer flask which is incubated at 37°C for 30 minutes to 2 hours. The bacteria are then separated and aliquots are plated on minimal media for the detection of mutants and on supplemented media for relative survival. Figure 1 provides a representation of the pilot test presently used. Pilot tests are used to define more appropriate testing conditions, and definitive tests provide data from which mutagenicity is judged. For complete testing, the substance must be tested in several strains of bacteria to monitor for a variety of different types of genetic alteration.

SYSTEMS OVERVIEW

This program uses TSO and was written in COBOL with some additional FORTRAN being integrated into the final program. All programming was accomplished on an IBM System/370 at the Division of Computer Research and Technology within the National Institutes of Health, Bethesda, Maryland.

For ease of programming, the task was divided into three individual programs (Figure 2). Information, needed prior to testing of a particular substance, is stored with the use of Program 1. This program also supplies a number for the blind coding of the compound. The second program provides for the technician the proper form of the basic protocol, performs certain "within-experiment" calculations, accepts the input of data from the tests, and evaluates the test by predetermined objective criteria. The ability for the central laboratory to monitor the accomplished work and recall any pertinent data is provided by Program 3. A more precise description of the program is available.[3]

Quality Control Through Interactive Computerization

One of the basic premises of quality control is that good data yields good decisions. By monitoring the quality of data during an experiment and providieng feedback to the technical personnel, both personal bias and technical variation can be reduced. With an interactive computer network this can be done. This pilot project demonstrates these capabilities in several ways. First, the compound to be tested is coded and only essential information for the test is provided. Secondly, certain other variables, e.g., concentrations of various components, are predetermined for both the pilot tests and definitive test. Within this testing system, two pilot tests are conducted to determine levels of toxicology and potential mutagenicity. From this data a narrower range of concentrations for the definitive tests are calculated by predetermined rules so that there are a limited number of

definitive concentrations used across all laboratories. Next, the computer performs any needed calculations during the performing of a test thus lessening the occurrence of potential computational errors. Some of the calculations performed for this system are: (1) bacteria per ml solution based on a standardized spectrophotometer curve, (2) variance for the weights of animals used in microsomal S-9 preparation (if outside normal limits, these will be rejected), (3) calculation of liver weights and amounts of buffers to be used in microsome preparation, and (4) calculations for the dilution of samples. Final data validation is also performed automatically upon the final data output. The computer's ability for data storage and retrieval is very important in this regard. For example, in this system, final results are recorded as number of colonies per plate. This software program compares the average number of colonies per plate for the controls to the past 100 accumulated controls to determine statistically if the controls are within normal limits. After the statistical examination of the controls the test is either accepted or rejected. If the test is a pilot then the data is also used to determine the concentrations of test substance to be used in further testing. All data is, however, recorded permanently. Rejected data is recorded so that an analysis of problems encountered can be done. A flow diagram for the areas within the decision processes is shown in Figure 3. The TSO is the component that allows for immediate technician/program interaction, thus allowing for a rapid and constant qualtiy control.

This prototype system demonstrates that interactive computer programs can be used to effectively increase the quality control of rapid *in vitro* tests. However, it is also apparent that the more simple *in vitro* microbial mutagenesis tests such as spot tests and simple plate incorporation tests do not require such extensive computerization if well documented and detailed protocols are available. Since most *in vivo* mammalian systems have extended experimental time periods, the time sharing option would be of little benefit due to cost factors and experimental design. However, even with the more simple *in vitro* tests and mammalian cell culture tests, this system can serve as a model for data storage and test evaluation for the purpose of quality control.

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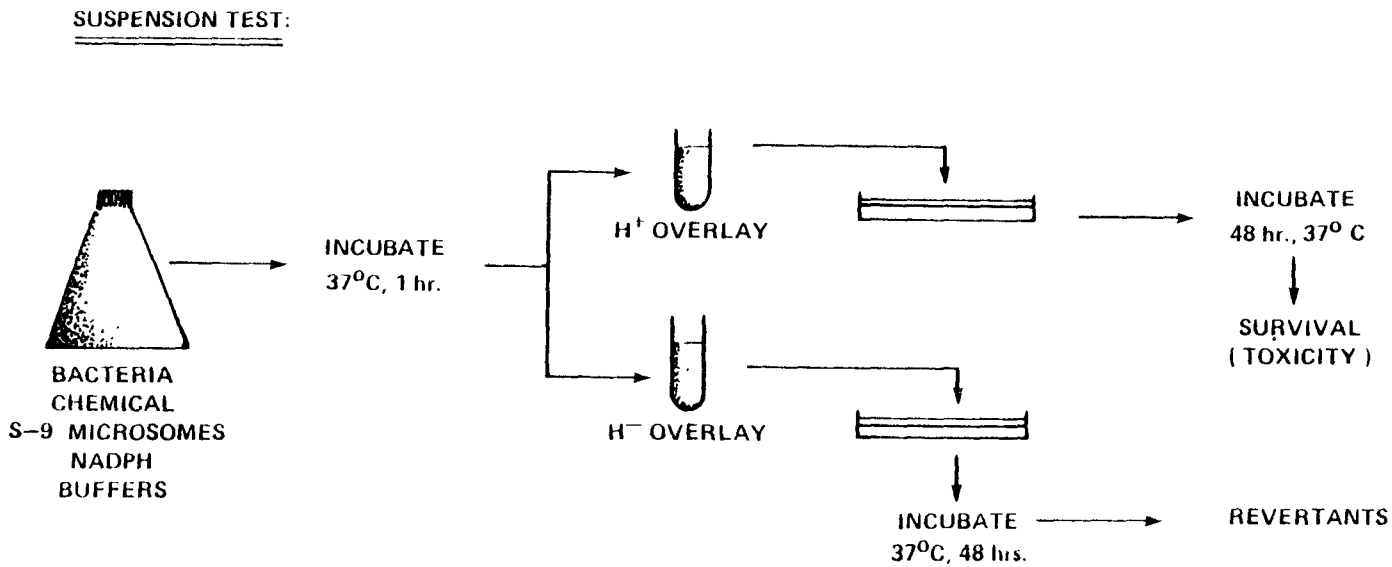

Figure 1: Diagramatic Representation of the Microbial Suspension Test for Mutagenicity.

The abbreviations used are as follows: NADPH, Nicotinamide-adenine dinucleotide phosphate; S-9, 9000 x G supernatant; H^+, supplemented with histidine; H^-, not supplemented with histidine.

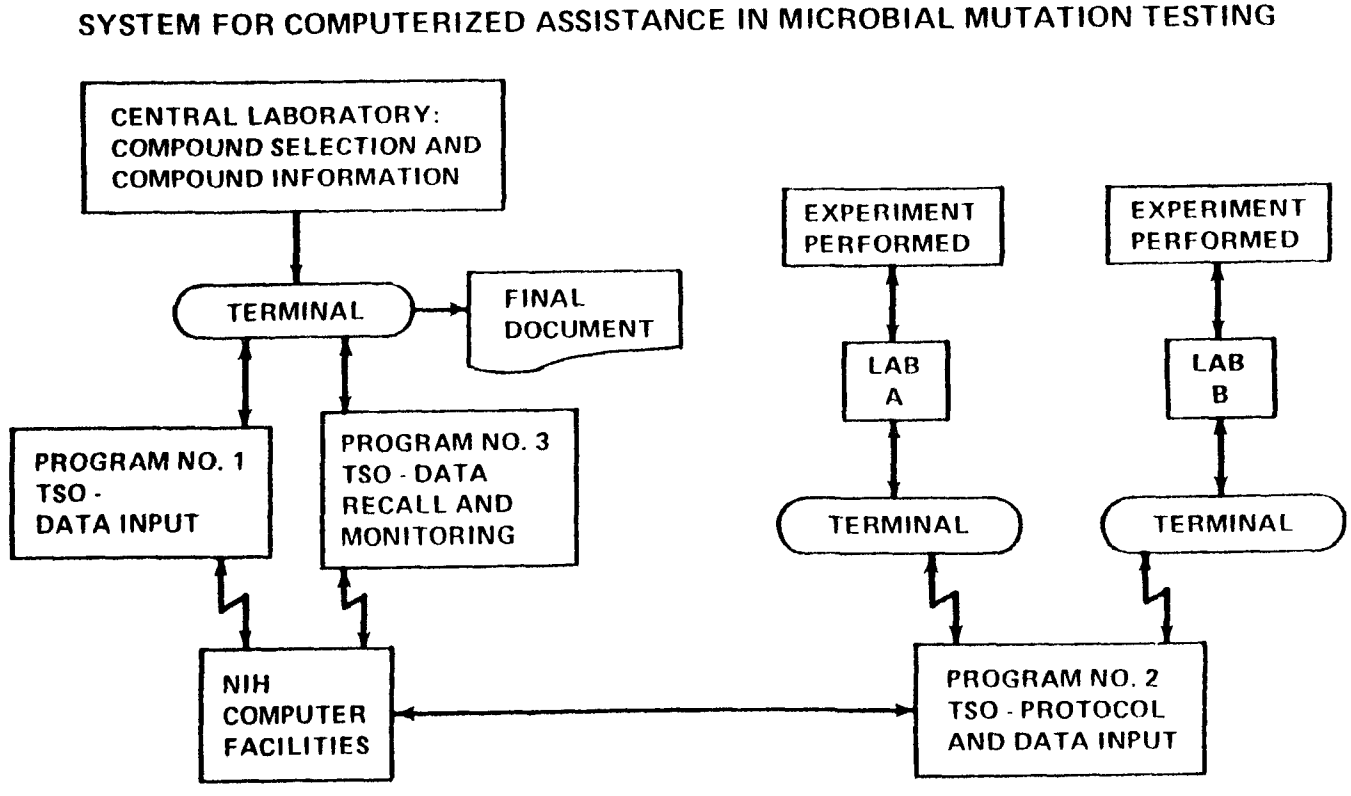

Figure 2: A System Flow Chart For the Computer Assisted Microbial Mutation Testing.

The abbreviations are as follows: TSO, Time Sharing Option; NIH, National Institutes of Health.

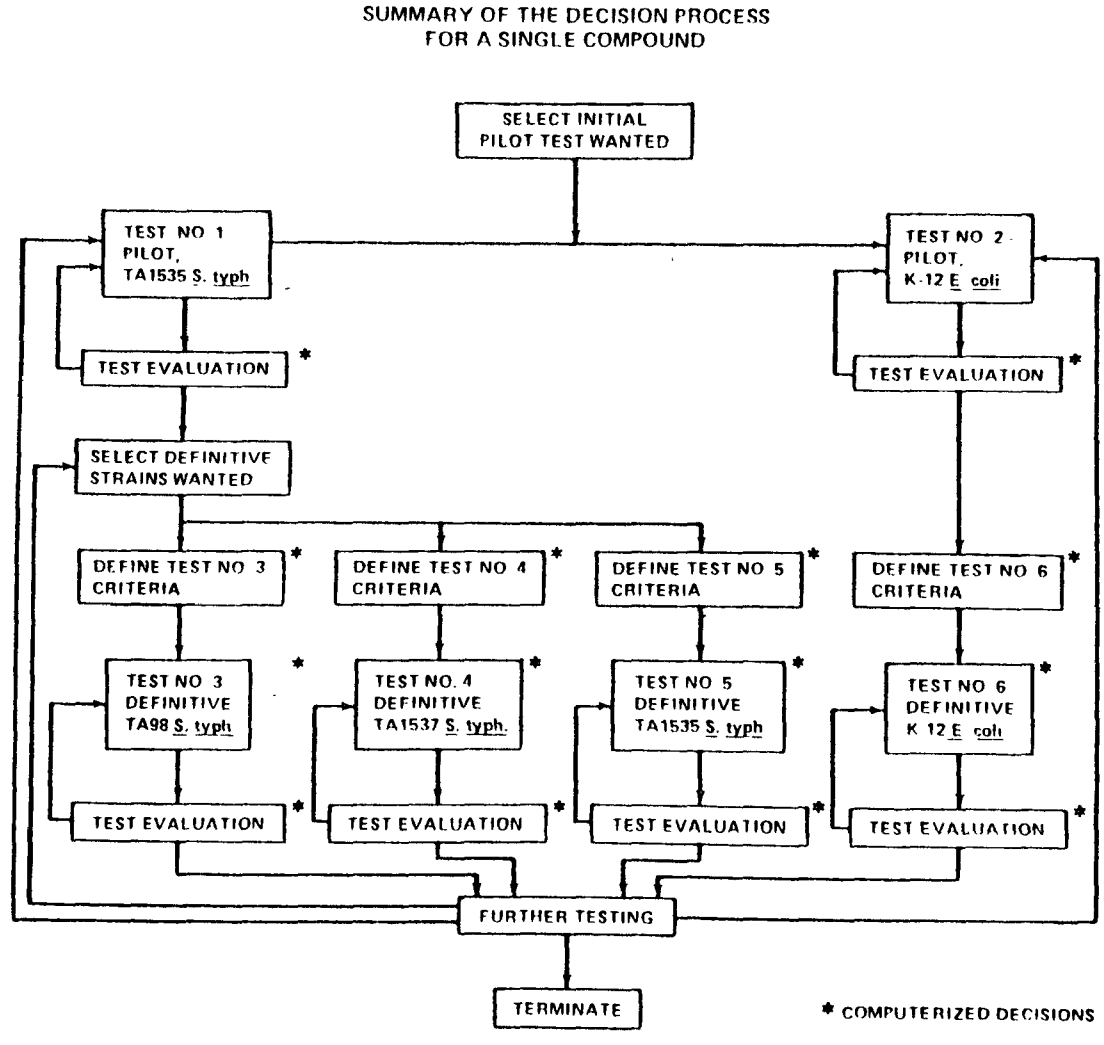

Figure 3: The Decision Process Flow Diagram

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16. ABSTRACT

Since health and regulatory decisions are being based upon the results of many short term tests conducted in many laboratories, a computerized system for an assurance of quality control would be valuable. This paper presents how quality assurance controls were included within the computer programming for a short term test -- the Salmonella suspension assay for mutagenesis.

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