Evaluation of an Information Retrieval System for Assessment of Toxicological Effects of Chemicals on Fish, Wildlife, and Ecosystem Components†

C. R. WALKER* and C. M. MENZIE

Division of Ecological Services, U.S. Fish and Wildlife Service, Department of the Interior, Washington, DC 20240

W. A. BOWLES, JR.

Denver Wildlife Research Center, U.S. Fish and Wildlife Service, Denver, Colorado 30225

Received August 6, 1980

A user-oriented information retrieval system is needed for assessment of materials hazardous to fish, wildlife, food chain organisms, and other organisms essential to the maintenance of ecosystem processes and functions. Critical evaluation of data also requires rigorous documentation of test conditions, precision of methods used, and the sensitivity of the test organism. Particular emphasis of the evaluation was in developing practical criteria that aid in the use and interpretation of data with respect to need for further testing in a scoring exercise performed for the Toxic Substances Control Act Interagency Testing Committee. Recommendations are made for the integration of information on physical and chemical properties, health effects, ecotoxicology, and environmental concentration or exposure level.

INTRODUCTION

Although the U.S. Fish and Wildlife Service evaluated some chemicals prior to 1941, these studies were accelerated greatly by funding from the Office of Scientific Research and Development and the Office of the Quartermaster General during and immediately following World War II.[1-3] The more sophisticated screening programs that evolved from these studies placed emphasis on relating chemical structure to selective forms of biological activity.[4-12] These later studies involved a variety of projects, which included the development of chemicals that might be useful for controlling those fish, birds, and mammals that are vectors of disease noxious forms of behavior that damage property, crops, and health of man and livestock. In more recent years the screening programs developed, in cooperation with the chemical industry, a number of substances that were useful for the enhancement of fish, wildlife, and their habitats or the control of animal populations and diseases which may affect the health of these populations.

As of 1965, about 100 different compounds were used in the management of fish and wildlife.[13] Since then, much of our research effort was redirected to generate data required by the regulatory agencies of fish and wildlife for registration and clearance of (1) drugs used for the control of diseases, (2) anesthetics for the management and culture of fish populations, or (3) pesticides for controlling pest species of fish, invertebrates, rodents, and birds. These regulations required our developing a large data base relating a number of different ecological effects of these control agents.[8,13-19]

THE TOXICOLOGICAL DATA BASE

The biological activity of 10 000 to 20 000 chemicals has been evaluated by U.S. Fish and Wildlife Service programs, as illustrated in Tables I–III. These programs were designed to find selective toxicants that would be effective control agents for nuisance species of wildlife, such as blackbirds or rodents, and fish, such as carp or lamprey.[2-5,8] Food acceptance testing listed in Table I was important in the discovery and development of toxic baits. Those chemicals that were found to repel animals also had practical application in the protection of trees, seeds, crops, and materials. Table II lists tests required to develop chemicals for controlling animal populations. These tests were conducted at the Patuxent and Denver Wildlife Research Centers. Studies were designed to evaluate the effectiveness of candidate toxicants and to minimize adverse effects on nontarget organisms.[7,8,12,20] These programs

Table I. Number of Chemicals Processed for EPA HEEDA[a] from those Tested by U.S. Fish and Wildlife Service Laboratories[b]

source	compounds tested	compounds processed
Patuxent Wildlife Research Center "Blue Book" Food acceptance test	~4200	0
Patuxent Wildlife Research Center "Red Book" Food acceptance test	2700	0
Toxicity test	1000	0
Patuxent Wildlife Research Center "DeWitt-Quartermaster Corps"		
Toxicity test	908	908
Leetown Research Laboratory		
e. M. Wood Project	4000	0
	total ~7000	908

[a] U.S. Environmental Protection Agency Health and Environmental Effects Data Analysis program. [b] Testing was performed in cooperation with the Chemical-Biological Coordination Center.

Table II. Number of Chemicals Processed for EPA HEEDA[a] from the Number Tested by the U.S. Fish and Wildlife Service in the Damage Control and Pesticides Hazard Assessment Programs[b]

	compounds tested	compounds processed
bird project	~2500	~1600
mammal project	~3600	~600
repellency project		
mammalian tests	~1200	0
plant tests	<1200	0
pesticide-wildlife studies		
toxicity tests	~200	106
residue chemistry	~50	*c*
	total ~7000	

[a] U. S. Environmental Protection Agency Health and Environmental Effects Data Analysis program. [b] Tests conducted at the Denver Wildlife Research Center. [c] On tape in the Denver Wildlife Research Center's Chemical Residue Analysis System.

† Presented on April 23, 1980, as a part of the Symposium on Development and Use of Reliable Data Bases for Quantitative Structure–Activity Relationships (QSARs) during the 14th Middle Atlantic Regional Meeting of the American Chemical Society, King of Prussia, PA.

Table III. Number of Chemicals Processed for EPA HEEDA[a] from the Number Tested by the U.S. Fish and Wildlife Service through Federal Aid to Fish Restoration State Projects or Under Contract to Conduct Aquatic Toxicology Studies

source	compounds tested	compounds processed
Hammond Bay Biological Station	~8000	4346[b]
National Fishery Research Laboratories, La Crosse, Columbia	~2500	*b*
	~500	*b*
Columbia River Development Program, University of Idaho	1888	*c*
Gulf Breeze (now EPA)	~500	*b*
Federal Aid to Fish and Wildlife Restoration, Missouri, New York	~500	0
	1496	1496

[a] U.S. Environmental Protection Agency Health and Environmental Effects Data Analysis program. [b] Some on tape in the U.S. Fish and Wildlife Toxicological Data System. [c] In progress.

were complemented by research and monitoring activities to assess the ecological effects of pesticides and related chemicals on fish and wildlife.[13,21-35] Some of the data generated by these activities are also listed in Table III and have been incorporated into the U.S. Fish and Wildlife Service Toxicological Data System (FWSTDS).[36] This user-oriented system has been modified to accommodate the Chemical Abstracts Service (CAS) registry number for entering data into the U.S. Environmental Protection Agency (EPA) Health and Environmental Effects Data Analysis (HEEDA) program in cooperation with the University of Pennsylvania Department of Computer and Information Science.[37] The major problem in developing information for inclusion in HEEDA was the acquisition of the CAS registry number and accuracy of the entry of information into a retrievable form—one that could be useful to the user of that data. At the same time this had to be a highly disciplined system that would allow a house evaluation for a critical examination of the methodology used in generating this information.

Thus far, approximately 7500 of the 20000 chemicals, formulations, and mixtures have been screened for biological activity by the U.S. Fish and Wildlife Service and their contractors or the federal aid programs.[38] Tables I–III illustrate the various kinds and sources of toxicological data from our projects involving the control, by toxicants or repellents, of plants, fish, invertebrates, birds, and mammals. Also listed in Tables II and III are data on effects on fish, wildlife, and food organisms of more than 500 formulations of pesticides. This information has been generated in laboratories located at Columbia, MO; Denver, CO; Gulf Breeze, FL; Hammond Bay, MI; La Crosse, WI; Patuxent, MD; and Warm Springs, GA; contract or federal aid studies have been done at the Missouri Conservation Commission, New York Department of Environmental Conservation, and the University of Idaho. About 3300 compounds from the Denver Wildlife Research Center have been entered into the HEEDA in the FWSTDS format. These include 908 compounds from the Quartermaster Corps project, 1600 compounds from our bird project, 600 compounds from the mammal project, and 106 compounds from the pesticide studies. We also have a considerable amount of data on residue and metabolism chemistry in the Denver Wildlife Research Center's Chemical Residue Analysis System (CRAS) that we are currently considering for possible conversion to HEEDA.

On the aquatic toxicology side (Table III), we have an extensive bioassay program that was initiated several years ago in cooperation with the Canadian government to develop

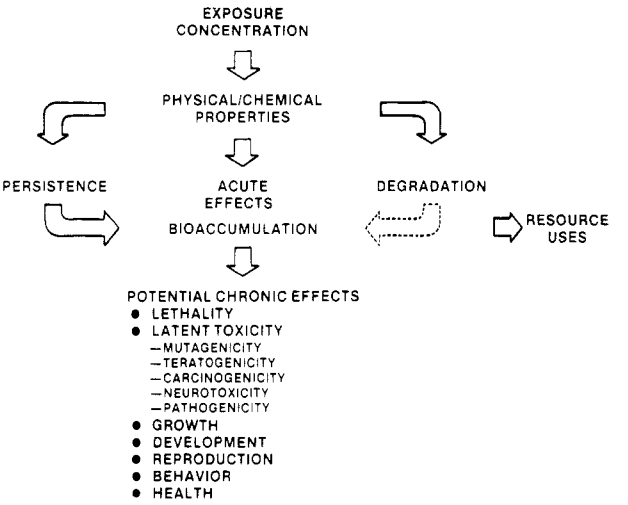

Figure 1. A tiered sequence of testing for toxicological effects. Such testing must consider the fate and persistence of a chemical affecting the acute effects, bioaccumulation, metabolism, chronic effects, and resources related to the ecosystem components. In this system "acute effects" refer to lethality (selective toxicity can have beneficial and adverse ecological effects).

a selective toxicant for controlling the parasitic sea lamprey. This program generated acute toxicity data on four species of fish in range-finding tests involving 8000 compounds. Thus far, 4346 of the compounds have been entered into this system. From our national laboratories at La Crosse, WI, and Columbia, MO, we have toxicity data on additional 3000 chemicals, formulations, and mixtures. Much of this information is stored in FWSTDS on magnetic tapes. We are converting these FWSTDS chemical codes into CAS registry numbers for inclusion in the HEEDA system. We also have toxicity data in the FWSTDS from the former U.S. Fish and Wildlife Service laboratory at Gulf Breeze, FL, that eventually became an EPA laboratory. This data base contains about 500 compounds, including tests on shellfish species as well as marine and estuarine fish. We have also processed about 1500 of the 2000 compounds screened in our federal aid programs by the states of New York and Missouri.

In a U.S. Fish and Wildlife Service study contracted to the University of Idaho for the development of a selective toxicant for squawfish, we developed toxicology data on 1888 compounds in bioassays on four different species of fish, including salmonids.

EVALUATION OF ECOTOXICOLOGICAL DATA

During the appointment of one of the authors (C.R.W.) to the Toxic Substances Control Act Interagency Testing Committee as the Department of the Interior representative, he became aware that many tests were inappropriate in their application to a particular need. First of all, if one examines a chemical to evaluate its potential benefit or use, one needs to know something of its environmental release and have an accurate estimate of the amount and duration of exposure to organisms in that environmental compartment (Figure 1). Hazard assessment of chemicals requires integrating information in Tables IV and V on the physical and chemical properties with the manner in which this material degrades and impacts in the environment within the organism's population or community. We are compelled to determine the biological significance of realistic routes and levels of exposure in terms of an acute effect and a chronic effect. Needless to say, the organisms used in a test system must accurately simulate the expected conditions of exposure and environmental compartment; the organisms used in the test system also must be sensitive enough to demonstrate the effect at the

Table IV. Testing on Lowest Level of Organization in the Ecosystem[a]

level of organization	environmental compartment		
	air	water	soil
organisms	exposure chamber tests with higher plants (also seedings) and lichens inhalation tests with mammals and birds rarely, tests with lower animals tests with bryophytes criteria: pathological anatomy, growth, respiration, photosynthesis	tests with organisms such as mollusca, annelida, polychaeta, crustaceae, echinodermata, pisces; majority of tests is with fish criteria: mortality and occasionally growth or reporduction rarely, tests with hydrozoa and macroalgae	pot experiments with higher plants tests with organisms such as collembola and lumbricidae criteria: mortality, growth rarely, tests with other animals such as microarthropods and nematodes

[a] Exposure concentrations and test systems simulate environmental compartment and utilize species sensitive to the mode of action of the chemical.

Table V. Testing on Higher Levels of Organization in the Ecosystem[a]

level of organization	environmental compartment		
	air	water	soil
populations	occasional experiments with bacteria and algae	reproduction tests with microorganisms (bacteria, fungi, microalgae, protozoa) or with microalgae, crustacea, and fish	tests with bacteria, soil algae, and protozoa
communities	microcosms, e.g., moss carpets, lichen vegetation, turfgrass	microcosms with zooplankton and phytoplankton, fish experiments with pond communities	"litter-bag" (gross heterotrophic decay) microcosms with soil communities pot experiments with mixed vegetation

[a] Populations and communities may be tested when ecosystem functions are at risk from the environmental concentration of the toxic substance.

concentration and conditions of exposure, as well as the level of organization in the ecosystem, as illustrated in Table VI. Thus it is very important that the precise description of the test conditions, genetic history of the test organisms, and their health, vigor, and prior exposure to chemicals be documented.[8,14,39-41] No amount of statistical manipulation of data can compensate for poor experimental design and lack of consideration for both determinate variables and limitations inherent in biological test systems. We need to say a few words about the necessity of using caution in the interpretation of data and how information may be used in hazard assessment. Generally speaking, when information is not critically evaluated, it has a tendency to be misused. We strongly recommend that competently trained ecotoxicologists be involved at both the input end and the user end of the computer.

Several authors have developed methods for estimating environmental exposure and information critical to a hazard assessment program.[42-52] However, one problem with such studies is that toxicity data may not match up with the route of exposure.[17] For example, a rat oral LD_{50} may be of limited value if the route of exposure is by inhalation, and, conversely, a material with high vapor pressure can hardly be adequately tested in a static bioassay for fish toxicity. Thus many of the customary types of bioassays or screening tests are completely inappropriate when we consider the physical and chemical properties of the substance. Another pitfall is the lack of understanding of the ecological fate of a substance and the significance of degradation and transformation of the toxicant. Very often in the water environment we fail to look in the right place or comprehend compartmental residue dynamics and rate of metabolic processes. Although biomagnification through food chains is rare, bioaccumulation occurs in many instances. The fact that the fish gill separates the environmental chemistry of the water from the internal blood chemistry of the fish is not fully appreciated relative to the physiologic functions of these poikilotherms. Temperature has a profound effect on the rates of metabolism, rates of uptake, depuration, and toxic nature of chemicals in these cold-blooded animals. Also, the external environmental chemistry can be extremely variable in its chemical constitution with regard to such important features as pH, dissolved gases, and solids. Slight changes in the integrity of the gill can be reflected almost immediately by the response within the fish. Also the physiological function of the "blood brain barrier" in various species of fish is easily violated by compounds producing an anesthetic response. Since we have developed many anesthetic agents for use on fish, we think it is an excellent experimental organism for screening chemicals that may have effects on the central nervous system.[39,40,53-55] When fish "bioaccumulate" enough chemical, the anesthetic effects prevail, and the fish recover following the "depuration" of residues, upon return to freshwater, or following metabolization or excretion of sufficient amounts of the chemical. However, the capability of fish to accomplish this varies among species. Species differ in bioaccumulation rates, and the rates differ with different compounds.[45,50] Some chemicals are more persistent, while others are more readily degraded and form metabolites or transformation products that have biological implications for ecosystem compounds and humans. Transfer of toxicological information between ecological testing and health effects testing is needed, particularly with regard to toxicants that affect reproduction, behavior (neurotoxicity), mutagenicity, etc.[56-60] For example, the Ames tests include bacteria and invertebrates for mutagenicity testing that are significant in

Table VI. Integrated Concept of Ecological Effects of Toxic Substances on Structural and Functional Aspects of Each Level of Organization[a]

level of organization	examples of effects	
	structural aspects	functional aspects
biomolecules	DNA defects	impairment of repair and replication; increased mutation rate
cells	chromosome defects	impairment of cell metabolism
tissues	histopathology, tumor formation	functional impairment
organs	pathological morphology, teratogenicity	functional impairment
organisms	pathological morphology, dwarfism	impairment of growth; mortality
populations	sex ratio; age distribution	impairment of reproduction
communities	loss of diversity	loss of stability

[a] Required in computer modeling of hazard assessment.

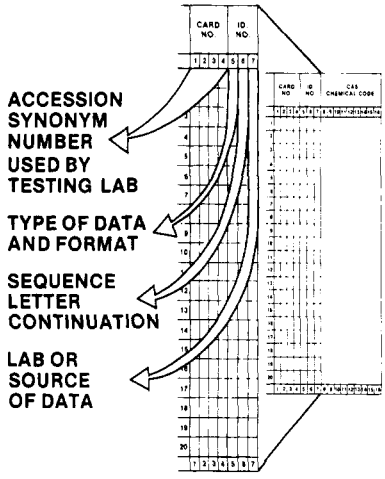

Figure 2. An illustration of the coding method used for designating the laboratory synonym or assession number and type and source of data in relation to the Chemical Abstracts Service (CAS) registry number.

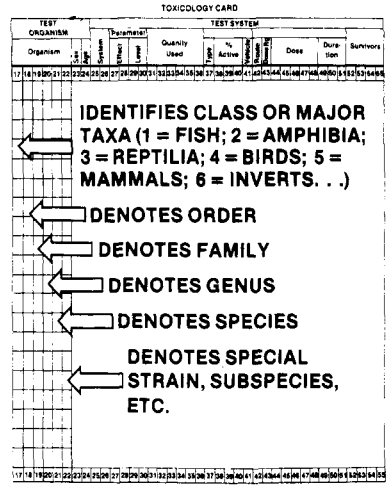

Figure 3. The codification of the name of the test organism, a systematic nomenclature in which each column is a cipher for the taxonomic level of organization for card columns 17–22 entered from a glossary of scientific names. Other glossaries are alphanumeric quantifiable entries for each subfield from card columns 23–55.

evaluating adverse effects of a chemical on microorganisms and various carbon reduction, mineralization, and plant nutrient processes. However, the mutagenic effect involving DNA repair and chromosomal damage in the mudminnow (*Umbro limi*) should have much greater biological significance in human health testing than the Ames test utilizing the fruit fly (*Drosophila melanogaster*). Koeman et al.,[59] Klingerman,[61] and others have utilized the mudminnow to measure mutagens in the Rhine river water. Kenaga[44,45] has also been able to statistically analyze the comparative toxicity of a variety of chemicals on fish, birds, rats, algae, and various invertebrates, including insects. Kenaga was able to predict toxicity of certain classes of chemicals to one general taxon such as birds, on the basis of toxicity tests run on another taxon, such as mammals or fish. However, these studies and others[8,60] demonstrated that the rat is not nearly as sensitive a test organism to many toxicants as are birds, fish, or invertebrates such as the water flea (*Daphnia magna*).

Thus the evaluation of chemicals affecting behavior, reproduction, growth, and development should receive more attention than tests that use acute lethality as an end point. Also, as suggested in Tables IV–VI, the maintenance of the integrity of the level of organization or ecological function can be tested in simulated laboratory or field monitoring studies that uniquely distinguish ecotoxicology from human safety testing. Model ecosystem testing and computer-based simulation models are also gaining popularity, but we need a great deal more good quantitative chemical data combined with ecotoxicity testing to validate these methods.[62–64]

FISH AND WILDLIFE SERVICE TOXICOLOGICAL DATA SYSTEM

An interlaboratory effort was initiated in 1966 to develop an electronic data-processing program that would handle the toxicological information generated by the U.S. Fish and Wildlife Service. The team of investigators responsible for the initial studies included Jack Lowe (now of the EPA, Gulf Breeze, FL, Environmental Research Laboratory), Walter Bowles (Denver, CO, Wildlife Research Center), James DeWitt (Patuxent, MD, Wildlife Research Center), John Howell (Hammond Bay, MI, Biological Station), and Charles Walker (La Crosse, WI, Fish Control Laboratories). From this effort a comprehensive system was developed for cataloging our toxicological data. (This system is described in an unpublished report by Menzie, DeWitt, Walker, and Bowles.[36]) The system has been evaluated by the present authors and modified as follows to accommodate the CAS registry number (CAS No.) and data accession/location code in the primary search field comprising columns 1–16 (Figure 2). The "Card No." field (columns 1–4) is used for the synonym number assigned by the laboratory for the sample, batch, or formulation actually tested by the investigator. The "ID No." includes the type of data and format in column 5, followed by the sequence letter for continuation of data in column 6, which is then followed by the code designating the laboratory or source of data in column 7. The CAS No. is entered into columns 8–16. Columns 79–82 also serve as an addendum for information on test numbers, series, or observations.

The next major field, columns 17–55, is for the description of the test system and results. Figure 3 illustrates the type of information displayed in columns 17–22 in which the systematic name of the test organism is entered by using a large catalog developed through our U.S. Fish and Wildlife Service laboratories associated with the Smithsonian Institution. The taxonomic integrity is as important to the biologist as the correct chemical name is to the chemist. Thus, utilizing this systematic way of naming we can identify the major class, the order, the family, the genus, the species, and even the strain. The other column headings are self-explanatory, with a glossary provided for each column to code data essential in describing the test system. Special attention, however, must be given to documenting the control for environmental quality listed in columns 59–64 (Figure 4). In this example, an aquatic test requires documentation of temperature in column 59, pH in column 60, and water hardness, alkalinity, or salinity in column 61. Specific references describing the details of the test methods are given in columns 65–68 and 70–78.

EVALUATION OF DATA FOR HEEDA

Column 69 is reserved for designating the type or quality of the data entered into the system in the form of a house evaluation code explained in Table VII. The assigned value is made by a consensus among the scientists involved with the development of the data. Thus, at this pre-"Good Laboratory Practice-EPA" stage, a numeric entry is used in column 69. We strongly advocate the use of standardized or consensus methodologies, for example, those of the American Society for Testing and Materials, Committee E-35 on Pesticides. Eventually we will have an alphanumeric code to enter in this column to designate an EPA-approved "Good Ecotoxicological (Laboratory) Practice." However, the state of the art as currently practiced must be evaluated as good, mediocre, or

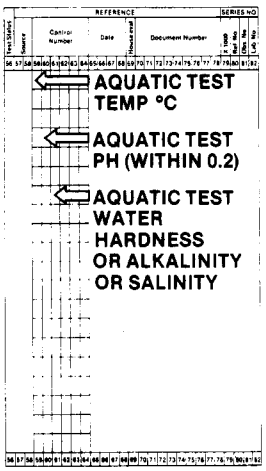

Figure 4. One example of a critical rating factor for the house evaluation criteria. The essential documentation required in card columns 59–61 is the test temperature, pH, and water quality parameter for aquatic testing. Other codes in this field are subjective and include glossaries or abbreviated information on the reference or source of test data.

Table VII. Card Column 69, House Evaluation Criteria[a]

code	qualitative criteria
	Statistically Calculated Dose–Effect Relationship from Published Form
9	with minor deficiencies or conditional acceptance by GLP[b]
8	with major deficiencies
7	unspecified methods or with major deficiencies
6	unknown source
	Range-Finding Test
5	known source, in published form, with specified methods, minor deficiencies, accepted standard methods of GLP[a]
4	known source, in published form, with specific methods, conditional acceptance by GLP[a] or standard methods
3	known source, in published form, with specific methods, but with major deficiencies
2	known source, with specified methods, but with major deficiencies
1	known source, but unspecified methods
0	unknown method or source

[a] Required for weighting the biological significance of data in terms of methodology used, quality of data, and statistical adequacy. [b] "Good Laboratory Practice".

bad and graded accordingly. The tests conducted with replicate controls, statistically calculated values, and careful documentation of the determinate variables get high scores. Much of the bird information that we enter from our Denver laboratory, for example, would score an 8. There are many tests, however, among the mammalian range-finding tests that would score only perhaps a 2. This evaluation is first done by the person or persons who generated the information; it then passes into review with the other scientists that are their peers in this area. If it is not done in this fashion, it will get a lower value than it would have if the author had, in his way, justified the way the tests were run and the validity of the data to his peers on the House Evaluation Panel. Much of the information generated in the range-finding tests are not statistically calculated and from the known source would at best get a score of 4, since conditionally accepted methods are used only in range-finding tests. Thus the best scores we will see here coming out of four former screening programs would rank in the 2–4 range. But it does help a great deal to know what the validity of that data would be and how it might be interpreted.

In Figure 5 any blank or lack of documentation in those critical areas previously mentioned in the toxicology field automatically results in a lower score as a major deficiency. For example, if the formulation or the percent purity is unknown, the data becomes suspect and result in a major deficiency. In the case of aquatic toxicology, or terrestrial toxicology, we have specific physical, chemical, and biological criteria that must be met to make those tests understandable or interpretable. Therefore, their validity is suspect until the author can justify to the House Evaluation Panel that these parameters were not, in effect, a limitation to the interpretation of that information. Thus far, we have had no difficulty among our scientists in agreeing upon the parameters that are critically important and those that are conditional. Although we are able to move forward with the transfer of this information from the laboratory bench into the system, there is grave reservation regarding the qualifications of people who will interpret this information. Thus caution is needed in this particular area, and a follow-up user-education process is required. This is particularly necessary if this information is to be used correctly and validly applied in the hazard assessment process or in developing structure–activity relationships.[65-69] Since we know we have limited test facilities, we need to move forward in testing those compounds that are of the highest priority. Hopefully, computer modeling of structure–activity relationships will allow us to guide priorities in testing.

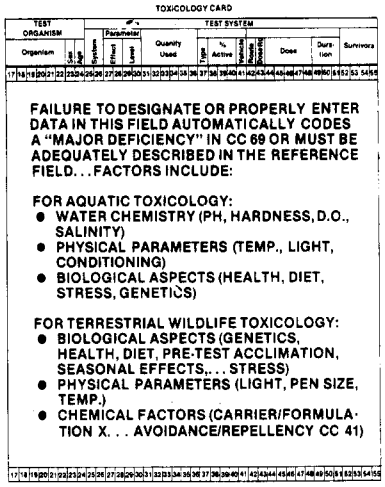

Figure 5. Illustration of how the house evaluation criteria may be further modified or downgraded when the documentation is incomplete. A major deficiency is identified if the essential factors are missing.

ACKNOWLEDGMENT

This project was financially supported by the U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances, under the interagency agreement EPA-IAG-79D-X0833.

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The GENE-TOX Program: Genetic Activity Evaluation†

MICHAEL D. WATERS*

Genetic Toxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

ANGELA AULETTA

Office of Testing and Evaluation, Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC 20460

Received July 31, 1980

The GENE-TOX program, a two-phase evaluation from the existing literature of selected bioassays for detecting mutagenicity and presumptive carcinogenicity, is described. Sponsored and directed by the Office of Testing and Evaluation within the U.S. Environmental Protection Agency's (EPA) Office of Pesticides and Toxic Substances, this program will aid EPA in establishing standard genetic testing and evaluation procedures for the regulation of toxic substances and determining the direction of research and development in the area of genetic toxicology.

INTRODUCTION

The GENE-TOX program (evaluation of current status of bioassays in genetic toxicology) is a systematic scientific evaluation of selected bioassays currently used for detecting mutagenicity and presumptive carcinogenicity of chemicals. This program is sponsored and directed by the Office of Testing and Evaluation (OTE) within the Office of Pesticides and Toxic Substances (OPTS), U.S. Environmental Protection Agency (EPA). Its primary purpose is to aid EPA in establishing standard genetic testing and evaluation procedures for the regulation of toxic substances. On a broader scale, the data compiled through this program and its appraisals of existing methodology for determining mutagenicity and presumptive carcinogenicity will be invaluable to scientists working in genetic toxicology and related areas.

In regulating the release of toxic substances into the environment, EPA and other agencies attempt to determine the mutagenic or carcinogenic potentials of a wide variety of environmental chemicals. The more than 100 inexpensive short-term bioassays now in use, while not yielding conclusive evidence, can indicate which chemicals should be more thoroughly investigated through long-term, whole-animal studies. However, the results of such assays for a given chemical or class of chemicals are frequently incomplete, inconclusive, or conflicting. Discrepancies arise from differences among the bioassays in their sensitivity and applicability to various classes of chemicals and differences among investigators in experimental protocols and techniques of data analysis and interpretation. EPA thus frequently lacks the necessary information to permit definitive conclusions concerning a chemical's possible mutagenicity or carcinogenicity.

It is desirable that mutagenicity and related testing required under the Toxic Substances Control Act (TSCA), the Federal Insecticide, Fungicide, and Rodenticide Act, and other Federal legislation be standardized and regulatory personnel be provided objective criteria by which to evaluate test results. Furthermore, it is essential that existing literature be made available in a readily usable form. Through the GENE-TOX program, selected literature on the most useful and relevant bioassays is being assembled, evaluated, and placed in a computer file for rapid retrieval and analysis.

The assays to be evaluated were selected on the basis of their genetic end points (e.g., primary DNA damage, gene mutation, or chromosome aberration) and the number and kinds of chemical compounds for which the assays have been used. Although some of the bioassays have been used with relatively few chemicals, they have been included because of their unique roles in the evaluation of genetic effects; for instance, an in vivo system might be a primary tool in risk assessment, or a certain test might be especially sensitive in detecting a particular type of genetic damage. The performances of the assays are to be compared on a chemical-by-chemical and class-by-class basis. This information will be used by EPA in designating batteries of tests for mutagenicity evaluation of chemicals by means of a sequential testing scheme. It will also bring to light areas in which additional test system development and validation are most urgently needed.

ORGANIZATION AND OBJECTIVES

The GENE-TOX program includes two phases: (1) work group evaluation of individual bioassays and (2) summary evaluation and assessment, which will address a series of

† Presented on March 24, 1980, as part of the Symposium on Development and Use of Quantitative Structure–Activity Relationships (QSARs) during the 179th National Meeting of the American Chemical Society, Houston, TX, and on April 23, 1980, as part of the Symposium on Development and Use of Quantitative Structure–Activity Relationships (QSARs) during the 14th Middle Atlantic Regional Meeting of the American Chemical Society, King of Prussia, PA.