Toxicology Information Systems: A Historical Perspective

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Toxicology information systems have evolved swiftly from early, library-based bibliographic tools to advanced packages utilizing sophisticated computer and telecommunication technologies. These systems have evolved concurrently with the rapid expansion of the science of toxicology itself. Bibliographic files such as TOXLINE represent first attempts to handle the toxicology literature through on-line retrieval. Subsequent approaches applied the use of computers to provide literature-derived data, as in TDB or RTECS, or to capture data directly in the laboratory. Societal concerns about hazardous substances, manifested in legislation and regulations, have been responsible for the creation of many computerized systems. Advanced, integrated information management systems are being explored as a method of accessing a large number of independently maintained toxicology databases. Changes in information technologies such as the trend toward microcomputers and novel high-density storage devices will affect the future of toxicology information systems as will impending developments in toxicology itself related to biotechnology, analytical methodology, and alternatives to whole animal testing.

INTRODUCTION

The field of toxicology has witnessed an unprecedented growth within the past 25 years. This explosion in subject matter, stemming largely from social concerns and matched by equally rapid technological innovation, has resulted in a serendipitous marriage between toxicological information and advanced systems to collect, organize, and distribute this information. This paper will briefly define toxicology and historically trace the state of toxicology information systems from precomputer days through current computer files and on to future projected systems. Representative systems will be described. A sidelong glance will be cast at the impetus, often regulatory, for the generation of toxicological information. Readers seeking a more detailed review of toxicological information and its resourcers are directed to a recent paper by the same authors.[1]

Toxicology deals largely, though not exclusively, with the effects of chemicals on biological systems. Toxicological information takes many forms: raw laboratory data (quantitative, qualitative, and descriptive), field data (e.g., poisoning incidence, workplace hazard monitoring), journal articles and books, statutes and regulations, etc. Toxicology information systems arrange portions of these data in a concerted plan or to serve a common purpose. Although the word "system" has become strongly identified with computers, as it will be throughout most of this paper, card files, libraries, and organizational networks (e.g., poison control center networks) may all loosely fall into the category of systems. One of the main difficulties for designers of toxicology information systems has been the interdisciplinary nature of the field. Toxicology borrows heavily from chemistry, biology, pharmacology, and other sciences, and a major challenge has been to manage this dispersed information efficiently.

EARLY HISTORY

One of the key documents in this field is the 1966 Report of the President's Science Advisory Committee entitled "Handling of Toxicological Information",[2] referred to here as the PSAC Report. Surveying the status of toxicological information prior to and up to the time of this report will make its findings and recommendations all the more illuminating.

Throughout the first half of the century, toxicology was frequently considered a subset of pharmacology. A 1960 paper considering whether toxicology was an independent scientific discipline, pointed out that "...our toxicology is an infant, barely emerged from the womb of pharmacology. We do not fully know how to utilize our strengths and talents."[3] Similarly, at this time, whatever toxicology instruction existed was usually presented within the context of a pharmacology course, and there was no full-scale toxicology Ph.D. program operating.[4] National attention was focused on existing and new pharmaceutical products, related poisoning incidents, and the need to ensure the safety of these and other consumer products.

The 1938 Food, Drug and Cosmetic Act required an assessment of drug safety before distribution. Between 1959 and 1962, thousands of deformed babies were born in Western Europe as a result of mothers taking the drug thalidomide early in pregnancy. The 1962 amendments to the Food, Drug, and Cosmetic Act, passed partly in response to this tragedy, strengthened testing requirements.

While the debt of toxicology to pharmacology was undisputed, the expanded role that toxicology would play in broader environmental issues was starting to be recognized. A 1960 conference entitled "Problems in Toxicology"[5] brought together distinguished scientists who addressed not only food, drug, and cosmetic control but environmental chemicals, pesticides, industrial chemicals, radioactive materials, and more. The Chairman of this conference, in his opening remarks, stated, "Toxicity is suddenly upon us as a social problem."[6] However, it took 2 more years with the 1962 publication of *Silent Spring*[7] for the public to be jolted into an awareness of the dangers associated with the uncontrolled production and use of thousands of chemicals. That chemicals could produce chronic effects, sometimes not apparent until years after exposure, was a stunning revelation to the American public. The environmental movement was conceived in the 1960s and burgeoned in the 1970s; toxicology became caught up in its tide.

What was the state of toxicology information systems in the early 1960s and mid-1960s? Informal communication among scientists and professional meetings were, as they still are today, important means of transmitting new findings. Among the earliest journals in the field—still linked to pharmacology—were the German *Sammlung von Vergiftungsfaellen* (1930), the Russian *Farmakilogiia i Toksikologiia* (1938), and the Danish *Acta Pharmacologica et Toxicologica* (1945). In the U.S., the journal *Toxicology and Applied Pharmacology* (1959) was to become the official organ of the Society of Toxicology, founded in 1961. Many new toxicology journals would be born thereafter.

Published toxicology information was largely library based. Indexing and abstracting tools for the major disciplines were

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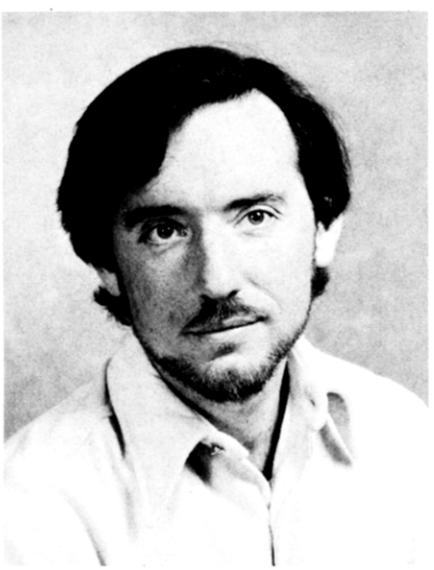

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well-established. Such reliable standards as *Biological Abstracts*, *Chemical Abstracts*, *Excerpta Medica*, and *Index Medicus* offered means of tracking toxicology literature, albeit in a limited way by today's standards. All of these bibliographic tools would eventually see their automated counterparts, for widespread availability of computer technology was on the horizon. The batch-processed MEDLARS (Medical Literature Analysis and Retrieval System) became operational at the National Library of Medicine in 1964 followed by MEDLINE, the on-line version of *Index Medicus* in 1971. Still, there were no information systems dedicated to serving the toxicologist, to pull together and make readily accessible the far-flung data being generated by increased testing and appearing in an increasing array of publications.

In the aforementioned PSAC Report,[2] the PSAC Panel expressed its concern about the dispersion of toxicological information over a large area of the published journal literature, published and unpublished reports, and unpublished information files of industrial companies and government agencies. The Panel's major finding was that "there exists an urgent need for a much more coordinated and more complete computer-based file of toxicological information than any currently available and further, that access to this file be more generally available to all those legitimately needing such information."[8] The Panel also provided a useful definition of toxicological information as "all information descriptive of the effects of chemicals on living organisms or their component subsystems."[9] The recommendations of the PSAC Panel led, in 1967, to the establishment of the Toxicology Information Program at the National Library of Medicine (NLM).[10]

ADVENT OF COMPUTER DATA BASES

Bibliographic Systems. TOXLINE, the earliest on-line bibliographic system for toxicology, was developed by NLM's Toxicology Information Program in 1972 as a "one-stop shopping center" for bibliographic information in toxicology. The original intent to follow the MEDLINE lead and "mechanize" an existing abstracting and indexing (A&I) source for on-line bibliographic retrieval had to be adjusted because no one secondary source covered the field of toxicology sufficiently. It was decided, therefore, to combined "toxicology subsets" from various A&I services into one file that would look reasonably homogeneous to the on-line user. Thus, TOXLINE initially incorporated relevant segments from *Index Medicus*, *Biological Abstracts*, *Chemical Abstracts*, and *International Pharmaceutical Abstracts*. Over the years, other segments have been added while some had to be deleted.[11,12]

TOXLINE also served to validate the utility of whole-text searching without a controlled vocabulary. This was accomplished by creating one large inverted file of all searchable terms.

Over the years, TOXLINE has grown to over 1.4 million records, has been divided chronologically into a current file and two backfiles, and now has over 10000 h of on-line usage per year. Because of the continued rapid growth of the literature in this field, TOXLINE did not reach its goal of being the "one-stop shopping center" for toxicology. Indeed, it has been shown by several authors that for really comprehensive searches in toxicology, other on-line data bases such as *Biological Abstracts*, *Chemical Abstracts*, and *Excerpta Medica* must be consulted as well.[13,14]

Because toxicology is concerned with the effects of chemicals on biological systems, the accurate identification of the chemical substance(s) involved in a toxicologic event is a critical preliminary to utilizing toxicology information systems. For TOXLINE, this problem was met by building an on-line companion file, CHEMLINE, that derived its content mainly from the Chemical Abstracts Service (CAS) Registry System. CHEMLINE[15] became the first of the "on-line chemical dictionaries" that link nomenclature, structural information, and CAS Registry Numbers to the location of information about specific chemical or groups of structurally related chemicals in other files. CHEMLINE made two fundamental contributions to chemical information retrieval: it demonstrated the importance of the CAS Registry Number in on-line

information seeking, and it showed that the fragments derived from parsing standardized chemical nomenclature could provide useful on-line substructure retrieval capabilities.

As the drive for computerization of its entire production system continued at CAS, larger portions of the CAS Registry System were made available to on-line information distribution organizations, such as DIALOG[16] and SDC,[17] which mounted CHEMNAME and CHEMDEX, respectively. This process culminated, in a sense, when CAS made the entire CAS Registry System accessible for on-line search as the new service CAS ONLINE.[18]

While the TOXLINE paradigm of a bibliographic service devoted to toxicology was not used by other information providers, many of the on-line files generated by the secondary services that covered the biomedical literature naturally included references to the literature in toxicology. Numerous studies comparing on-line retrieval from TOXLINE with that from other on-line bibliographic services have been reported.[13,19-21]

Systems for handling the bibliographic information of specialized areas of toxicology have also been developed. Examples here are the files of the Environmental Mutagen Information Center (EMIC) and the Environmental Teratology Information Center (ETIC);[22] both files are available on-line through TOXLINE and the U.S. Department of Energy's RECON system. The cancer-related literature, including carcinogenesis, is accessible through CANCERLIT and EXPRESS on the NLM system. A good source for information on pesticides and their toxicology can be found in the National Agricultural Library's AGRICOLA, available from DIALOG, BRS,[23] and SDC.[24,25] The literature of occupational exposure to chemicals is covered by NIOSHTIC, an on-line file produced by the U.S. National Institute for Occupational Safety and Health and the CIS file of the International Labour Office (not to be confused with CIS, the Chemical Information System) available on-line through QUESTEL[26,27] and partially on TOXLINE.

Data or Fact Retrieval Systems. Bibliographic retrieval systems—on-line or in printed form—are fact locators in that they direct the user to journal articles or books that contain the sought-for facts. In contrast, data or fact retrieval systems—like handbooks—provide the user with the actual facts (i.e., they are "fact providers"). While "data" and "fact" are here used synonymously, the name fact retrieval systems is perhaps more appropriate for this discussion since "data" often connotes numeric values, while so much in toxicology represents observations that must be described in words.

Early examples of literature-derived factual data banks in toxicology, still available on-line, are the U.S. Government sponsored systems TDB (Toxicology Data Bank), RTECS (Registry of Toxic Effects of Chemical Substances), and OHMTADS (Oil and Hazardous Materials Technical Assistance Data System).

The TDB, built and operated by NLM, was started in 1978 to provide users on-line, interactive access to evaluated toxicological data. Some of the decisions made in designing this data base touch on general issues that have to be considered in building data retrieval systems.

In order to obtain "evaluated" data for TDB, data statements were extracted from monographs and handbooks rather than from the primary journal literature. This was based on the assumption that the intellectual filtering process taking place while moving information from primary journals to tertiary sources will select proven or reasonable observations over those that are more speculative or are contradicted by later observations. Nonetheless, TDB is now being augmented with data from the primary literature because, for some chemicals, the monographic sources generally used for the file do not contain sufficiently up-to-date information.

TDB contents are further screened by a committee of toxicologists, the TDB Peer Review Committe, before they are released on-line.[28] This serves as a means of quality assurance, a critical feature of any data system intending to provide accurate and reliable information. The Committee is an offshoot of the National Institutes of Health (NIH) Toxicology Study Section, which has as its main function the evaluation of grant applications in the area of toxicology. This Committee has successfully transferred the consensus development methods used in grant review to the evaluation of toxicological data extracted from the literature.

The TDB, with over 60 data elements and 4000 compound records, is organized as a matrix of compounds and their chemical, physical toxicological, and environmental attributes. TDB contains such information about compounds that are hazardous and to which there is significant human exposure. This project has been described in several papers.[29-31]

The *Registry of Toxic Effects of Chemical Substances* (RTECS) is a compilation which provides brief descriptions of substances for which acute or other toxic effects have been reported in the literature. RTECS also provides nomenclature, CAS Registry Numbers, and some mutagenic, teratogenic, and carcinogenic effects data, as well as references to government regulations and standards. While RTECS is still issued as a publication[32] in hard copy as well as on microfiche, its machine-readable equivalent has been available for several years for on-line access from NLM and the Chemical Information System (CIS).[33] The RTECS Editorial Review Board reviews a limited number of citations to resolve ambiguities. However, file content in general is not peer reviewed.[32]

OHMTADS is a data bank, developed by the Environmental Protection Agency (EPA), to provide data about compounds that might become involved in chemical spills. It carries some 126 data elements and describes over 1200 compounds.[34] OHMTADS content is also not peer reviewed. The file is available on-line on the CIS system.

Computerized systems to collect and process biological data developed during research and testing are becoming more prevalent.[35,36] One such system, developed by the National Center for Toxicological Research, allowed collection, processing, and analysis of large-scale, rodent-based tests.[37] Beckman Instruments, Inc., developed this approach further into a free-standing data collection and processing system called TOXSYS, consisting of both specialized hardware and specialized software.[38] Another system for the collection and processing of data from large-scale animal experiments has been reported by the German Center for Cancer Research.[39]

Most such data collecting and processing systems are intended for support of research and testing in a given organization, and the resulting data banks are not usually accessible to outsiders. However, one system, the Laboratory Animal Data Bank (LADB), developed and tested by NLM, was created to compile laboratory results for control animals in hematology, clinical chemistry, and pathology from many laboratories and provide them to users on-line for analysis and reference.[29,40] The Project had to be terminated in 1981 because of funding cuts.

IMPETUS FOR TOXICOLOGY INFORMATION SYSTEMS

Having traced the evolution of toxicology information systems up to the present, it might be appropriate to pause and examine some of the reasons for their development, before exploring future directions. As alluded to earlier in this paper, there is a significant societal component to toxicology. While the public has, in one sense, benefited greatly from the growing number of chemicals in commerce, it has also become justi-

fiably fearful about hazards that these chemicals pose to man and the environment. These concerns have, in turn, expressed themselves in legislation at various levels.

These laws, and the regulations sprouting from them, have been an important influence on the creation of toxicology information systems. Affected societal groups had to install new information gathering and reporting procedures and this, in turn, has led to the development of new information systems and services. The rapid growth of computerized systems for information handling over the same time period naturally had a profound impact on the nature of these systems and services. Several Federal laws that influenced the formation of toxicology information systems are mentioned below.

The 1906 Food and Drugs Act was recast in 1938 as the Federal Food, Drug and Cosmetic Act. Its 1962 amendments, which were mentioned earlier, strengthened reporting requirements, resulting in increased generation of data related to efficacy, safety, and clinical experience, the maintenance of records, and the creation of corporate systems to handle these data.

The Occupational Safety and Health Act of 1970, among its provisions for protecting workers and adopting workplace standards, called for the publication of "a list of all known toxic substances by generic family or other useful groupings and the concentrations at which such toxicity is known to occur" [Section 20(a) (6)]. In compliance with this directive, the *Toxic Substances List* was published in 1971. This was the forerunner of the *Registry of the Toxic Effects of Chemical Substances* (RTECS), eventually to become the computer file discussed earlier.

The landmark 1976 Toxic Substances Control Act (TSCA) attempts to control the introduction, production, distribution, or use in commerce of any chemical that presents an unreasonable risk of injury to health or the environment. In response to the information gathering requirements of this law, the Interagency Toxic Substances Data Committee was organized and recommended the adoption of the Chemical Substances Information Network (CSIN) project described below. Another direct outgrowth of TSCA was the creation of the TSCA Chemical Substances Inventory, which currently lists some 70 000 chemicals in commerce; it is available on-line through DIALOG, and the chemicals are identified in CHEMLINE. Requirements for the extensive testing of chemical substances, as well as for the reporting and retention of information by manufactures, have resulted in the creation of numerous corporate information systems[41] and internal Environmental Protection Agency (EPA) files.

One of the more recent pieces of legislation, the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA, also known as the Superfund Act), authorized liability, compensation, cleanup, and emergency response for hazardous substances released into the environment and the cleanup of inactive hazardous waste disposal sites. It mandates the establishment of the Agency for Toxic Substances and Disease Registry, whose Administrator will "establish and maintain an inventory of literature, research and studies on the health effects of toxic substances" [Section 104 (i) (2)].

The above laws and others such as the Clean Air Act (1963), the Consumer Product Safety Act (1972), the Federal Insecticide Fungicide and Rodenticide Act (1972), the Resource Conservation and Recovery Act (1976), and the Safe Drinking Water Act (1977)[42] and the resulting regulations are responsible for many of the currently available governmental and private information systems ventures. Indeed, it has been suggested about toxicology that "the pressure from the regulatory arena...is driving the development and evolution of our discipline".[43]

DEVELOPMENT OF ADVANCED SYSTEMS

The sheer volume of toxicological literature and data, generated because of research, testing, legislation, or otherwise, is the immediate motivating factor for new information systems design. More than 100 journals currently devote most of their space to toxicology. Many specialized toxicology organizations now exist, and some 110 U.S. schools offer courses or programs in toxicology.[44] All in all, toxicology data and information have become more dispersed, not less, and there is, therefore, a greater need than ever before to order it in a logical manner.

Many other aspects of toxicology information systems, and especially those related to computer and communications technology, have also changed drastically over these last 25 years. In particular, the steady reduction in the cost of computer storage and the growth of the value-added communications networks such as Tymnet, Telenet, and Uninet that made the nationwide spread of on-line, interactive information retrieval systems possible have had major impacts on all scientific information systems including those in toxicology.

These technical developments created a market for the large, multifile on-line systems vendors such as BRS, DIALOG, and SDC. These vendors, using bibliographic files usually created by other organizations—such as the major A&I services—now provide the information user with an impressive array of information resources that cover the entire spectrum of the published scientific and technical information. While these organizations provide access to toxicological information, none of them has specialized in this area so as to be classified as a toxicology information system.

One on-line data retrieval facility that places emphasis on files relevant to toxicology is the Chemical Information System (CIS), which was created and supported by NIH and EPA.[45] For a while, EPA was the main supporter of CIS, but as of 1984, it has ceased this support. Instead, the system is being offered by two private-sector organizations.[46] The system is an aggregate of data files including RTECS and OHMTADS. The SANSS (Structure and Nomenclature Search System) file supports the identification of relevant compounds and classes of compounds with pointers to the availability of information on these compounds in other CIS component files. The Commission of the European Communities developed ECDIN (Environmental Chemicals Data and Information Network), a somewhat similar system, accessible through EURONET DIANE, TYMNET, and other facilities.[47]

Another approach to extracting toxicological information from large multifile on-line systems without being expert in the intricacies of the varied retrieval languages employed by these systems was developed by the CSIN (Chemical Substances Information Network) project.[48,49] CSIN consists of software and an "interface" computer through which the user accesses one or more on-line systems. Information collected from one system or file can be transformed in CSIN for use in the query statement posed to another system or file. Much of the searching for chemical and toxicological information can be performed with preprogrammed query statements called Scripts. The system was originally established in a VAX minicomputer and provided to users through a government-supported facility; this has recently been terminated because of lack of funding. However, the software, reprogrammed for microcomputers, is now being tested in free-standing applications.[50]

FUTURE OF TOXICOLOGY INFORMATION SYSTEMS

While prophecy is not considered a scientific discipline, predictions about future activities can reasonably be made by extrapolating present trends. Thus, it is safe to predict that toxicology information systems will be affected by changes in

two areas: (1) information technologies and (2) toxicology and related sciences.

Changes in Information Technologies. Over the last 25 years, information and data processing in the sciences have been changed fundamentally and irreversibly by the growth of computer technology. This growth can be expected to continue at a 20% annual rate for the next decade and beyond.[51] Therefore, further rapid and profound changes in the information field must also be expected. Many of these changes will, of course, also affect the future development of toxicology information systems.

While a detailed estimation of the nature of these changes is beyond the bounds of this paper, a few important trends can be mentioned, including (1) the rapidly spreading use of increasingly more powerful microcomputers as personal workstations, (2) the impending introduction of optical disc-based massive (over one gigabyte) local storage devices and information distribution systems,[52] and (3) the increasing use of on-line, whole-text searching of journals[53] and the coming into being of the "electronic journal".[54,55]

Changes in Toxicology and Related Sciences. Toxicology and its information systems are bound to be affected by the revolution now taking place in biology, "whose cornerstone is the technique of gene cloning",[56] and the related disciplines of biotechnology and genetic engineering. Since toxicology deals primarily with "adverse effects", it is those aspects of these new developments with which it will be concerned. Applications of these new technologies will involve the deliberate and—occasionally—the inadvertent release into the environment of organisms with new genotypes. The health and environmental implications of such events are beginning to be considered in Congressional hearings.[57] The impending use of gene therapy in humans[58] also may require changes in regulatory aproaches. Draft regulations for biotechnology products have been issued.[59]

Articles on these developments are being processed into the bibliographic retrieval systems by the relevant A&I systems. Separate services covering these areas also have been established (e.g., TELEGENLINE on DIALOG).[60] More basic changes in the applicable information methodologies also will have to take place. Up to now, the information support functions for toxicology focused on chemical substances. Information systems describing the impacts of biotechnology will have to encompass biological entities as well. Classification systems may have to be modified or created, and the techniques used for dealing with data and information relevant to biological entities may have to be applied. These new areas also will require new types of data banks and data handling methodologies. Initial examples here are the new NIH-supported computational resource for biotechnology, BIONET, and GenBank, a nucleotide sequence data bank.[61,62]

Biotechnology and advances in electronics and analytical chemistry are also producing ever more subtle analytical techniques to detect trace amounts of contaminants and evidence that biological systems have been exposed to xenobiotics.[63] Identification of populations at risk will become more finely tuned. We can expect refinements in analytical methodology to alter the course of toxicologic evaluations, as well as regulations and information systems.

Another aspect of toxicology presently undergoing scrutiny and changes is testing and research using whole animals. Widespread and increasing public pressure against the use of animals in research is bringing about the reappraisal and possible replacement of many presently used systems such as the Draize test in rabbits for eye irritation and the LD_{50} (lethal dose–50%) toxicity test.[64,65] The animal welfare movement advocating these changes is particularly influential in the U.S. and in other Western countries. Its efforts in this country have resulted in several animal welfare bills being considered by the Congress, some of which (e.g., H.R. 5098)[66] would have major impacts on present information systems.

New journals such as *Alternatives to Laboratory Animals*[67] are being published. We may see broader use of mathematical modeling and extrapolation techniques including Quantitative Structure–Activity Relationship (QSAR) methods[68] that could produce results comparable to those now obtained from certain animal tests.[69] Widespread replacement of whole animal toxicological testing will require changes in data collection, processing, and reporting systems.

Economic forces are also pushing toward changed toxicological test methods, particularly in long-term carcinogenesis testing using large numbers of animals. These 2-year studies are so expensive that the National Toxicology Program, the largest U.S. testing program in this field, can process only a few dozen compounds a year through full-scale carcinogenic evaluation. A variety of short-term tests to augment the present carcinogenesis tests are now being considered by that program.[70] Broad adoption of short term tests also would impact the supporting information systems.

Also imminent are the likely effects on some toxicology information systems of the new "Hazard Communication" (or "Right to Know") rule issued by the U.S. Department of Labor in 1983.[71] This rule, which has an implementation date of November 1985, and the many similar laws and regulations passed by over 20 States and municipalities require that workers be informed by their employers about chemicals to which they are being exposed in the workplace. Among other requiremens, the rule mandates written hazard communication programs, labels as hazard warnings, and extensive development of material safety data sheets.

To comply, chemical manufactures will have to make increasing use of toxicological data resources that emphasize workplace hazards and protective measures,[72,73] and market demands may make it possible for new data services in this area to be developed. It will be interesting to see whether the material safety data sheet—normally held in little regard as an information device because of a low level of scientific reliability—will now become more reliable and constitute an avenue for the dissemination of unpublished toxicological data and information residing in the files of chemical manufacturers.

Finally, as we contemplate the foreseeable changes in toxicology and its information systems, it is useful to remind ourselves that the information processed, stored, and retrieved is only as good as the research and testing that first developed the supporting data. Even in our "brave new world"[74] of supermicrocomputers with billions of bytes of stored information, the quality and reliability of the data and information are the basic requirements for good decision making and progress—in toxicology as elsewhere in science.

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