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Journal of Hazardous Materials 39 (1994) 225–243

JOURNAL OF HAZARDOUS MATERIALS

Information resources for chemical toxicology and regulation

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Abstract

During the last three decades, there has been an overwhelming increase in scientific and technical information. This information increase has heralded an age of unprecedented advancements in our knowledge about the toxicological sciences and the agents, particularly chemicals, that have been evaluated for the induction of untoward biological activity. Much of the information published is stored in computers in various forms for subsequent use and analysis. This information base, although an invaluable resource, presents an enormous challenge to those individuals requiring access to specific toxicology information for use in association with regulatory decision making. With large amounts of government funds being devoted to health and environmental research programs, the rate of growth for toxicology literature is expected to increase every year. To organize this growing literature and to make it easily accessible to users, different types of information systems have been developed. This paper focuses on those information systems that in the authors' opinions provide the best opportunity for accessing the toxicology literature for application in assessing potential human health hazards and chemical regulation.

1. Introduction

We live in an age of remarkable scientific and technical accomplishments. These accomplishments have brought unprecedented benefits to our standard of living and well being. Unfortunately, they also have brought insidious threats to human health and environmental quality. The extent of the concern regarding environmental pollution is evidenced by the introduction of numerous environmental regulations and guidelines at both federal and state levels. Federal and state governments must

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[1] Managed by Martin Marietta Energy System, Inc., for the US Department of Energy under contract No. DE-AC05-84OR21400.

SSDI 0304-3894(94)00050-Q

identify the potential threats from this environmental pollution, assess the associated risks, and provide guidance as to their prevention or regulation. Because most of the insults to human health and the environment come from chemicals, regulators must provide sound and reasonable hazard assessments for a variety of chemical agents that may have serious, far-reaching consequences. Information is required to make an assessment of a chemical's potential health risk or to determine how a chemical should be regulated. Because we live in an era where scientific and technical information is being generated in overwhelming quantities, an awareness of the key resources to use in accessing this information is necessary. This paper provides a discussion of and commentary on selected toxicology information resources that individuals may use in the process of assessing potential health risks.

2. Information resources providing access to the primary toxicology literature

Thousands of papers have been published on the exploration of a chemical's potential for inducing adverse effects on humans and the environment. Results from a recent query of the information files maintained by Chemical Abstracts Service regarding publication trends in the toxicology literature are shown in Table 1. Because the body of primary literature is so large, it is necessary to use one or more of the secondary information resources shown in Table 2 to screen effectively the literature available on a toxicological subject. To make maximum use of these secondary resources, users should consider carefully the content, coverage, scope, and quality of each to determine which suits the requirements of a given problem or issue. In the sections that follow, the authors provide a selection and analysis of key

Table 1
An example of the growth of the toxicology literature from publications catalogued by Chemical Abstracts Service

Year	Citations	Year	Citations
1967	924	1980	13657
1968	1046	1981	12827
1969	1590	1982	12422
1970	1863	1983	12196
1971	2392	1984	12525
1972	5549	1985	12236
1973	5780	1986	12246
1974	5593	1987	13090
1975	8293	1988	12410
1976	7975	1989	12623
1977	8340	1990	9876
1978	10605	1991	12584
1979	10901	1992	18677

Table 2
Sampling of secondary on-line bibliographic and/or numeric information sources containing toxicological information

Name	File, number of records, and period covered	File description
BRS Bibliographic Retrieval Services, Latham, NY	Biosis Previews 7196209 1969–present	Biosciences Information Service Worldwide coverage of research in the life sciences from more than 9000 journals, as well as monographs, reports, and symposia proceedings. Subjects include microbiology, plant and animal science, biochemistry, botany, environmental biology, experimental medicine, genetics, public health, toxicology, virology, and other interdisciplinary areas. Citations from both Biological Abstracts and Biological Abstracts/RRM
	CA Search 8900000 1967–present	Chemical Abstracts Service (CAS) Bibliographic data, keyword phrases, index entries, general subject headings, and CAS Registry Number(s) for documents covered by Chemical Abstracts Service
	HAZARDLINE 4000 substances	Occupational Health Services, Inc. Provides chemical names, formula, CAS Registry Number(s), Registry of Toxic Effects of Chemical Substances (RTECS) number, physical description, chemical and physical properties, toxicology, permissible exposure levels, symptoms of exposure, disposal methods, protective procedures, test references, government regulations, and many other areas of information on specific chemical substances
	MEDLINE MEDLARS On-Line 7000000 1966–present	National Library of Medicine Contains references from more than 3000 biomedical journals published throughout the world. Monographs and conference proceedings added in 1976. Corresponds to Index Medicus. Contains full bibliographic citations and index terms for all records. Some abstracts included. SDILINE, the monthly update to the main file, used for current awareness service
CAS online Chemical Abstracts Service American Chemical Society Columbus, OH	CAS online Chemical Serach System from Chemical Abstracts Service 8900000 1967–present	Equivalent of the printed Chemical Abstracts (CA). Bibliographic data, keyword phrases, index entries, general subject headings, and CAS Registry Number(s) for chemistry-related publications in 50 languages from 150 contries. Includes worldwide patent documents. Easy crossover to the CAS Chemical Registry

(*continued on next page*)

Table 2 (continued)

Name	File, number of records, and period covered	File description
	CAS Chemical Register 10000000 compounds	The world's largest file of substnace information, including coordination compounds, polymers, incompletely defined substances, alloys, mixtures, and minerals. In each record the registry number is linked to molecular structure diagram, molecular formula, CA index name, synonyms, and the ten most recent references in Chemical Abstracts. Easy crossover to the bibliographic file
DIALOG Dialog Information Services, Inc. Palo Alto, CA	EMBASE 4311401 June 1974–present	Excerpta Medica Abstracts and citations of articles from over 4000 biomedical journals published throughout the world. Covers entire field of human medicine and related disciplines
		Energyline Comprehensive coverage of 20 different energy-related areas, including environmental impact
		Enviroline Covers the world's environmental information by indexing and abstracting more than 5000 international primary and secondary source publications reporting on all aspects of the enviroment. Also includes rulings from the Federal Register and patents from the Official Gazette of the United States Patent and Trademark Office
	International Pharmaceutical Abstracts 175 587 1970–present	American Society of Hospital Pharmacists More than 650 pharmaceutical, medical, and related journals are indexed and abstracted
	Life sciences Collection 1254581 1978–present	Cambridge Scientific Abstracts Abstracts of worldwide literature in the fields of animal behavior, biochemistry ecology, entomology, genetics, immunology, microbiology, toxicology, and virology
	MEDLINE	See entry under BRS system
	NTIS	The National Technical Information Service (NTIS) is the central source for the public sale and dissemination of US government-sponsored research. The database consists of unclassified government-sponsored research, development, and engineering reports, as well as other analyses prepared by government agencies,

		their contractors, or grantees. The database corresponds to Government Reports Announcements and Index
	Occupational Safety and Health (NIOSH) 162316 1973–present	US National Institute for Occupational Safety and Health Technical Information Center Includes citations to more than 400 journal titles as well as over 70000 monographs and technical reports
	Pollution Abstracts	Pollution abstracts is a leading resource for references to environmentally related technical literature on pollution, its sources and its control. Produced by Cambridge Scientific Abstracts, the database corresponds to the printed Pollution Abstracts
	Scisearch 10029029 1974–present	Institute for Scientific Information Multidisciplinary index to the literature of science and technology, including animal and plant science, biochemistry, drug research, experimental medicine, and microbiology. Unique feature is indexing cited papers. Corresponds to the printed Science Citations Index
MEDLARS National Library of Medicine Bethesda, MD	CANCERLIT Cancer Literature 806157 1963 - present	National Cancer Institute Cancer therapy and chemical, physical, and viral carcionogenesis from *Carcinogenesis Abstracts and Cancer Therapy Abstracts*
	MEDLINE	See entry under BRS system
	RTECS 100000 chemicals	National Institute of Occupational Health and Safety Provides chemical names, formula, CAS Registry Number(s), RTECS number, physical description, chemical and physical properties, toxicology, permissible exposure levels, symptoms of exposure, disposal methods, protective procedures, test references, government regulations, and many other areas of information on specific chemical substances
	TOXNET Toxicology Data Network	A computerized system consisting of a collection of selected toxicology oriented data base and information files. Environmental Mutagen Information Center (EMIC) File. Environmental Teratology Information Center (ETIC) File Development and Reproductive Toxicology (DART) File Hazardous Substances Data Bank (HSDB) Chemical Carcinogenesis Research Information System (CCRIS)

(*continued on next page*)

Table 2 (continued)

Name	File, number of records, and period covered	File description
		US Environmental Protection Agency Genetic Toxicology Database (Gene-Tox) Registry of Toxic Effects of Chemical Substances (RTECS) Directory of Biotechnology Information Resources (DBIR) Toxic Chemical Release Inventory (TRI) Toxic Chemical Release Inventory (TRI) US Environmental Protection Agency Integrated Risk Information System (IRIS)
	TOXLINE Toxicology Information On-Line Current File: 1981 present > 100000 Backfiles (TOXBACK): 1980 and older material > 1160000	An extensive collection of toxicology information with references to human and animal toxicity studies, effects of environmental chemicals, pesticides, and pollutants, adverse drug reactions, and analytical methodology. Abstracts and/or indexing terms included in addition to full bibliographic citations. Information derived from secondary sources and special collections of material: Environmental Mutagen Information Center (EMIC) File Environmental Teratology Information Center (ETIC) File Epidemiology Information System (EPIDEM) Federal Research in Progress (FEDRIP) International Labour Office (CIS) International Pharmaceutical Abstracts (IPA) NIOSHTIC (NIOSH) Pesticides Abstracts (PESTAB) Poisonous Plant Bibliography (PPBIB) Toxicity Bibliography (from MEDLINE) (TOXBIB) Toxicology Document and Data Depository (NTIS) Toxicological Aspects of Environmental Healath (BIOSIS) Toxicology Research Projects (CRISP) Toxic Substances Control Act Test Submissions (TSCATS)
	TOXLIT and Toxlit65	A collection of bibliographic citations and abstracts assembled by the Chemical Abstracts Service under the title of Chemical–Biological Activities (CBC).The specific focus of this Collection is the pharmacological, biochemical, physiological, and toxicological effects of drugs and other chemicals

ORBIT System Development Corporation Santa Monica, CA	PESTDOC approximately 300000 1968–present	Derwent Publications Limited Covers worldwide journal literature on pesticides, herbicides, and plant protection. Includes analysis, biology, chemistry, and toxicology
	RINGDOC Pharmaceutical Literature Documentation approximately 1.2 million 1976–present	Derwent Publications Limited Covers scientific journal literature on pharmaceuticals. Specifically designed to meet the information requirements of manufacturers. Includes papers from over 750 worldwide journals
	VETDOC Veterinary Literature Documentation approximately 96000 1968–present	Derwent Publications Limited Covers journal literature concerning developments and usage of drugs, hormones, vaccines, growth promoters, etc., in farm and domestic animals. Includes analysis, chemistry, therapeutics, pharmacology, toxicology, and management

ETHYLENE DIBROMIDE

Chemical Abstracts Service Registry No. (RN) 106-93-4

Chemical Classifications (CCAT): Acyl halides, aryl halides, halogenated ethers and halohydrins, saturated alkyl halides, unsaturated alkyl halides

Test systems (TAX)

Prokaryotes – gene mutation	In vitro mammalian – gene mutation	Lower eukaryotes – other genotoxic effects
Lower eukaryotes – gene mutation	Plants – chromosome effects	In vivo mammalian, UDS – other genotoxic effects
Plants – gene mutation	In vivo mammalian somatic cells – chromosome effects	In vivo mammalian, sperm morphology – other genotoxic effects
Insects – gene mutation	Prokaryotes – other genotoxic effects	In vitro mammalian – cell transformation, viral enhancement

Species/cell type	Chinese hamster ovary (CHO) cells
Assay type	Forward gene mutation at the HPRT locus
Assay code	CHO +
Results	Positive
Panel report	EMICBACK/71517; Mutat Res 196:17–36, 1988
Reference	EMICBACK/45919; Mutat Res 95: 377–388, 1982
Species/cell type	Mammalian polychromatic erythrocytes
Assay type	Micronucleus test, chromosome aberrations
Assay code	MNTT
Results	No conclusion
Panel report	EMICBACK/77345;
Reference	EMICBACK/60491; Mutat Res 158: 81–87, 1985
Species/cell type	Aspergillus nidulans
Assay type	Forward gene mutation
Assay code	ASF +
Results	Positive
Panel report	EMICBACK/45086; Mutat Res 98: 49–94, 1982
Species/cell type	Syrian hamster embryo (SA7/SHE) cells
Assay type	Cell transformation, viral enhanced
Assay code	CT7 +
Results	Positive
Panel report	EMICBACK/50076; Mutat Res 114: 283–385, 1983

Species/cell type	Escherichia coli polA (W3119 vs P3478)
Assay type	Rec-assay, DNA effects (bacterial DNA repair)
Assay code	RE1 +
Results	Positive
Panel report	EMICBACK/45048; Mutat Res 87: 211–297, 1981
Species/cell type	Drosophila melanogaster
Assay type	Sex-linked recessive lethal gene mutation
Assay code	SRL +
Results	Positive
Panel report	EMICBACK/50912; Mutat Res 123: 183–279, 1983
Species/cell type	Saccharomyces cerevisiae
Assay type	Mitotic recombination or gene conversion
Assay code	YEC +
Results	Positive
Panel report	EMICBACK/52546; Mutat Res 133: 199–244, 1984
Species/cell type	Human
Sex	Male
Assay type	Sperm morphology
Assay code	SPH +
Results	Positive
Panel report	EMICBACK/50125; Mutat Res 115: 73–148, 1983

Species/cell type	
	Mouse lymphoma (L517Y cells)
Assay type	Forward gene mutation at the thymidine kinase (TK) locus; chromosome aberrations
Assay code	L51 +
Results	Positive
Panel report	EMICBACK/50691; Mutat Res 115: 225–251, 1983
Reference	EMICBACK/31144; Mutat Res 59: 61 108, 1979
Species/cell type	Neurospora crassa
Assay type	Forward gene mutation
Assay code	NEF +
Results	Positive
Panel report	EMICBACK/52327; Mutat Res 133: 87–134, 1984

Species/cell type	Nonhuman
Assay type	In vivo carcinogenicity studies (rodent assay)
Assay code	CCG +
Results	Positive
Panel report	EMICBACK/67174; Mutat Res 185: 1-195, 1987
Species/cell type	Mouse germ cells
SEX	Male
Assay type	Unscheduled DNA synthesis in male germ cells (UDT) in vivo; DNA effects
Assay code	UDT –
Results	Negative
Panel report	EMICBACK/58407; Mutat Res 134: 143–157, 1984

Fig. 1. Example of a Gene-Tox record with selected data/information categories.

resources that can be utilized effectively to address issues, problems, and questions on toxicology subjects.

2.1. *Peer-reviewed and evaluated information resources for chemical toxicology and regulation*

To effectively address the responsibilities associated with the regulation of chemicals, one must have access to reliable toxicological information resources. These should be of the type referred to as value-added or peer-reviewed toxicology resources. To provide insight into such resources, descriptions and commentaries are given for selected databases, information files, and publications dealing with genetic toxicology, carcinogenicity, and general toxicology.

US Environmental Protection Agency (EPA) Genetic Toxicology (Gene-Tox) database

The Gene-Tox database is a product of the EPA Gene-Tox Program [1, 2]. This activity was initiated in 1979 at the Oak Ridge National Laboratory (ORNL) for conducting a systematic evaluation of selected short-term bioassays detecting genotoxic activity and presumptive carcinogenicity. Sponsored and directed by the Office of Testing and Evaluation within EPA's Office of Pesticides and Toxic Substances, the Gene-Tox Program was conducted and coordinated by the Environmental Mutagen Information Center (EMIC) of the Biomedical and Environmental Information Analysis (BEIA) Section of ORNL. The Gene-Tox exercise provided a resource for use in establishing standard genetic toxicology testing and evaluation procedures for the regulation of toxic substances.

At the end of 1991, peer-reviewed information on over 4600 different chemicals had been entered into the Gene-Tox database. This information represents evaluation of these compounds in one or more of 64 genetic toxicology and 9 cell transformation assays or test systems.

The Gene-Tox database is available on-line through the National Library of Medicine's (NLM's) Toxicology Data Network (TOXNET) system [3]. Information from the Gene-Tox database is also included in chemical records of the Hazardous Substances Data Bank (HSDB), and locator tags are also placed with chemical records that are part of the Registry of Toxic Effects of Chemical Substances Database. Information about how to obtain access to the Gene-Tox database may be obtained by writing to the address shown for the HSDB on page 237.

The Gene-Tox database provides, in the author's opinions, the best and most reliable means to acquire an assessment of the genotoxicity of a chemical agent (Fig. 1). This resource is a suggested starting point when gathering information about a chemical's ability to induce damage to the genome of different organisms. Answers to several different types of questions, such as the following, are possible.

- What genetic toxicology data exist for a specific chemical?
- For which chemicals have certain specific mutagenicity assays been conducted?
- What chemicals or classes of chemicals are responsive (or unresponsive) in given test systems?

- What are the best assay systems to use to determine genotoxicity of a specific chemical?
- What assays are unlikely to give a good indication of the genotoxicity of a specific chemical?
- What is the likelihood that an untested chemical will be genotoxic based upon the known activity of chemicals that are structurally or functionally analogous?
- How predictive of mammalian in vivo genotoxicity are the in vitro assay systems?
- How predictive of heritable mutagenicity and of carcinogenicity are given assays?

International Agency for Research on Cancer Monographs

In 1971, the International Agency for Research on Cancer (IARC) initiated a program to evaluate the carcinogenic risk of chemicals to humans [4]. The object of the program was to provide government authorities with expert independent scientific opinions regarding environmental carcinogenesis through the publication of critical reviews of carcinogenicity and related data. The aim of IARC is to evaluate possible human carcinogenic risk from detailed review and analysis of pertinent literature.

The IARC Monographs summarize evidence for the carcinogenicity of individual chemicals and other relevant information on the basis of data compiled, reviewed, and evaluated by a working panel of experts (Table 3). Priority is given to chemicals, groups of chemicals, or industrial processes for which there is at least some suggestion of carcinogenicity, either from evidence of human exposure or from observations in animals. Note that the inclusion of a particular compound in an IARC volume does not mean that it is carcinogenic. As new data become available on chemicals for which monographs have already been prepared or as new principles for evaluation become available, reevaluations may be made at subsequent IARC meetings. If the new evidence warrants, revised IARC Monographs are published.

More than 1000 chemicals, chemical groups, or other agents have been reviewed by IARC. As of February 1993, 58 volumes of the IARC Monographs and several supplements had been published. These volumes contain indexes both for chemical name and molecular formula as well as Chemical Abstracts Service Registry Number(s). These monographs provide the best and most thorough review of chemical-induced cancer in animals. Carcinogenicity evaluations have not been made on all the chemicals reviewed because either the data were unavailable or the data were judged inadequate for evaluation. Specialized information files and databases developed at ORNL, such as the EMIC file and the Gene-Tox database, are used routinely by IARC in the production of their monographs. IARC Monographs may be obtained by contacting any bookseller through the network of World Health Organization sales agents. The IARC Monographs also are distributed internationally to governmental agencies, industries, and scientists.

Hazardous Substances Data Bank

The HSDB, formerly called the Toxicology Data Bank, originated at ORNL in the early 1970s under the sponsorship of NLM. HSDB is a numerical and factual database composed of over 4200 comprehensive chemical records [5, 3, 6]. These records contain approximately 140 different data elements that are grouped into 11

Table 3
Outline used to review agents evaluated for carcinogenicity by the International Agency for Research on Cancer

- Name of agent reviewed
  - Chemical and physical data
    - Synonyms
    - Structural, molecular formula, and molecular weight
    - Chemical and physical properties of the pure substance
    - Technical products and impurities
  - Production, use, occurrence, and analysis
    - Production and use
    - Occurrence
    - Analyis
  - Biological data relevant to the evaluation of carcinogenic risk to humans
    - Carcinogenicity studies in animals
    - Other relevant data
    - Experimental systems
      - Absorption, distribution, metabolism, and excretion
      - Toxic effects
      - Effects on reproduction and prenatal toxicity
      - Genetic and related effects
  - Human studies
    - Case reports and epidemiological studies of carcinogenicity to humans
  - Summary of data reported and evaluation
    - Exposure data
    - Experimental carcinogenicity data
    - Human carcinogenicity data
    - Other relevant data (genotoxicity, reproductive and developmental toxicity, general toxicity, structural activity correlations, etc.)
    - Evaluation
      - Evaluation of carcinogenicity in experimental animals
        - Sufficient evidence
        - Limited evidence
        - Inadequate evidence
        - Evidence suggesting lack of carcinogenicity
        - Supporting evidence of carcinogenicity (genetic effects structure–activity relationships, pharmacogenetics, etc.)
      - Overall evaluation for carcinogenicity in humans
        - Group 1 – agent is carcinogenic in humans
        - Group 2A – agent is probably carcinogenic in humans
        - Group 2B – agent is possibly carcinogenic in humans
        - Group 3 – agent is not classifiable regarding its carcinogenicity in humans
        - Group 4 – agent is probably not carcinogenic in humans

categories and administrative information. These categories include pharmacological and toxicological data (e.g., LD_{50} values), environmental and occupational information, manufacturing and use data, regulatory information, analytical methods, and information on the chemical and physical properties of each chemical. Components included in the toxicology category are shown in Table 4. Substances selected for HSDB include high-volume production or exposure chemicals; drugs and pesticides

Table 4
Data elements of toxicity and biomedical effects of the Hazardous Substances Data Bank, National Library of Medicine

Toxicity summary
Toxic hazard rating
Antidotes and emergency treatment
Medical surveillance
Toxicity excerpts
Human toxicity excerpts
Nonhuman toxicity excerpts
Toxicity values
Human toxicity values
Nonhuman toxicity values
Ecotoxicity values
Minimum human fatal dose
Populations at a special risk
Pharmacokinetics
Absorption, distribution, and excretion
Metabolism/metabolites
Biological half-life
Mechanisms of action
Interactions

exhibiting potential toxicity or adverse effects; and other substances subject to regulation under the provisions of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (Superfund) and the Superfund Amendment Reauthorization Act (SARA) of 1986.

The information used in an HSDB record is selected mostly from secondary sources such as standard reference books, handbooks, criteria documents, and monographs. The data extracted from secondary sources are reviewed quarterly by a scientific review panel (SRP) of experts convened by the NLM. Members of the SRP are professional toxicologists, industrial hygienists, and environmental engineers from academia or industry. Additional information from pertinent literature may be selected and developed on consensus statements on-line databases, such as TOXLINE (Toxicology Information Online), by the SRP and incorporated into an HSDB record to ensure that the record contains the most relevant and accurate information available. Records in the HSDB are, in the authors' judgement, the best on-line resources for obtaining information on the general toxicity of a chemical. Readers can obtain further information on the HSDB by contacting Specialized Information Service, Toxicology Information Program, National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894.

The US Air Force Installation Restoration Toxicology Guide (AFTG)

The AFTG was sponsored by the Harry G. Armstrong Aerospace Medical Research Laboratory at Wright–Patterson Air Force Base and prepared by staff of the BEIA Section of ORNL. It is a peer-reviewed, 5-volume document consisting of over 3500 pages devoted to a review of the toxicology of select chemical compounds (Table 5).

Table 5
Outline of parameters used to review agents included in the Air Force Installation Restoration Toxicology Guide

A. Name of agent
B. Synonyms
C. Reactivity
D. Physicochemical data
E. Persistence in the soil–water system
F. Pathways of exposure
G. Health hazard data
  - Signs and systems of short-term exposure
  - Acute toxicity studies
  - Long-term effects
  - Pregnancy/neonate data
  - Genotoxicity data
  - Carcinogenicity classification
    - International Agency for Research on Cancer
    - National Toxicology Program
    - US Environmental Protection Agency
H. Handling precautions
I. Environmental and occupational standards and criteria
  - Air exposure limits
  - Water exposure limits
  - Reference dose
  - Regulatory status
    - Promulgated regulations
      - Federal programs
      - State programs
    - Proposed regulations
      - Federal programs
      - State programs
J. Environmental fate and exposure pathways
  - Transport in soil/groundwater
  - Sorption on soils
  - Volatilization from soils
  - Transformation processes in soil/groundwater systems
  - Primary routes of exposure from soil/groundwater systems
  - Other sources of human exposure
K. Human health considerations
  - Animal studies
    - Carcinogenicity
    - Genotoxicity
    - Teratogenicity, embryotoxicity, and reproductive effects
    - Other toxicological effects
      - Short-term toxicity
      - Subchronic and chronic toxicity
  - Human and epidemiological studies
    - Short-term toxicological effects
    - Chronic toxicological effects
    - Hazard assessment
L. Sampling and analysis considerations

One of the objectives of AFTG is to provide individuals responsible for the management and implementation of the US Air Force Installation Restoration Program with information to evaluate the health hazards associated with actual or potential contamination of drinking water supplies. Volumes 1 through 4 of the AFTG contain information on 70 chemicals and complex mixtures of environmental concern to the US Air Force. Volume 5 contains similar information on 7 metals and over 80 environmentally significant compounds containing these metals. Data summary sections providing concise, easily accessible data useful to environmental engineers precede detailed environmental and toxicological review sections. These summaries include chemical names and synonyms; registry numbers; physicochemical data; information on reactivity and handling precautions; soil-water persistence; pathways of exposure; health hazard data; environmental standards and criteria; and state, federal, and European Economic Community regulatory status.

The toxicology review sections for each chemical in the AFTG include detailed information on acute, subchronic, and chronic toxicity data, as well as information on developmental toxicity, genotoxicity, and carcinogenicity. Environmental information for each chemical encompasses environmental fate and exposure pathways and fate and transport in soil and groundwater. A section on biological monitoring for each metal-containing compound is included.

Information on the AFTG may be obtained from Harry G. Armstrong Aerospace Medical Research Laboratory, Toxicology Division, Wright–Patterson AFB, OH 45433-6573, or by directly contacting the National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161, USA.

3. Recommended information resources for chemical toxicology and regulation

Peer-reviewed or peer-evaluated databases, such as those previously described, offer the most expedient and comprehensible toxicology information resources for use by risk assessors and those involved with chemical regulations. Most often, individuals who must assess the toxicity of chemicals are faced with tight schedules and must reach decisions quickly. These decisions must be supported by factual data, whenever possible, and with liberal applications of intuitive reasoning when the data are weak or nonexistent. It is our opinion that the first tier in the data/information selection process should include the resources reviewed in this section and supplemented with other resources from those listed in Table 2. This suggested process is illustrated in Fig. 2. Because there is a lack of peer-reviewed toxicity information on most chemical substances, the use of resources to support intuitive reasoning, such as chemical structure analysis, must be used. The next section discusses this activity.

3.1. The current status of using chemical structure as a tool for predicting biological activity

A considerable amount of activity is now focused on the way in which chemical structure influences biological activity. In the absence of experimental data, the

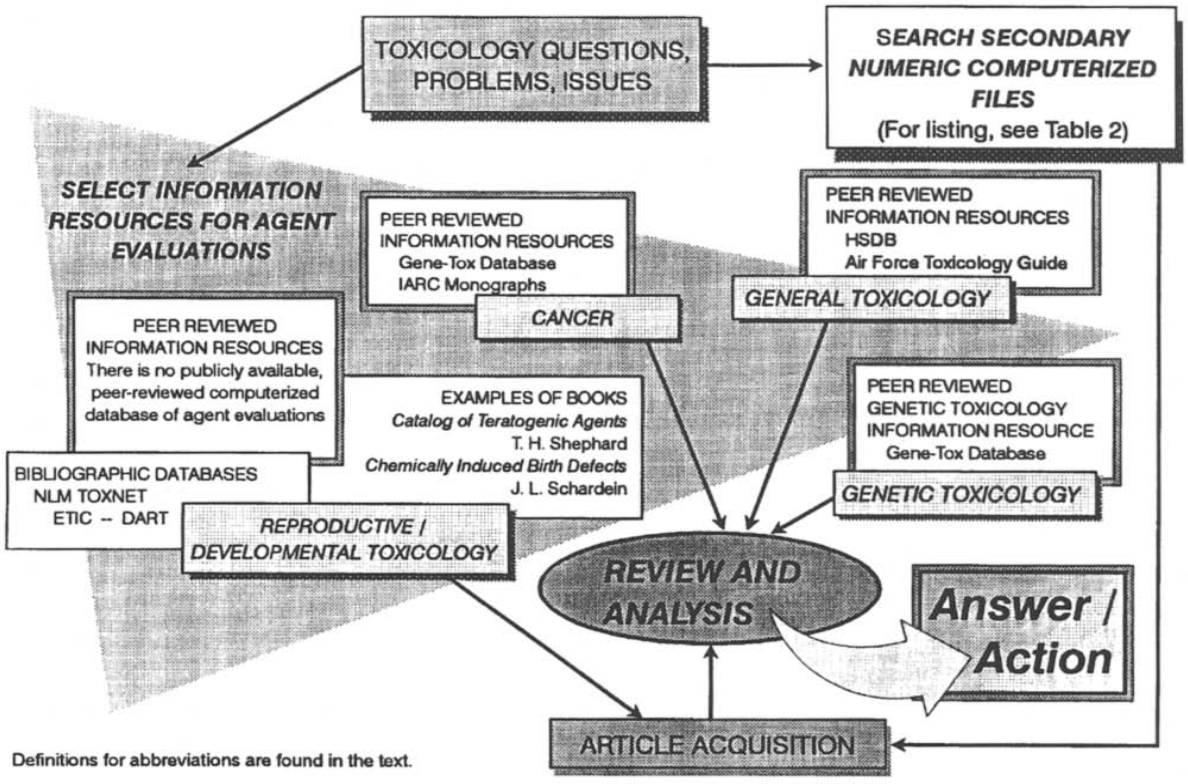

Fig. 2. Suggested procedures for effective use of toxicological information resources.

structure of a chemical is studied as a means of obtaining possible indications of potential hazards. Studies to develop machine-based systems that will allow one to make predictions of toxicological events from chemical structure are increasing. Several interesting techniques, models, and systems have been devised [7–9], but none of these have evolved into all-purpose systems for widespread application. This section provides a brief review of the structure activity relationship (SAR) concept as it relates to toxicology.

The correlation of chemical structure with biological activity is rooted in the early history of the pharmaceutical sciences when compounds with structures similar to known medicinal agents were selected to test their efficacy to combat human disease. The principles of drug action based on chemical structure have been carried over to the toxicological sciences, where structural characteristics of chemicals with known activity are compared with compounds whose activities are unknown.

Because the volume of toxicology literature has grown significantly over the years, an enormous information base on various toxicological endpoints is available for making comparisons of chemical structure with untoward biological activity. The information resources discussed in this paper can serve as valuable resources in SAR studies for particular endpoints, such as genotoxicity, carcinogenicity, and reproductive toxicity. Several other worthwhile databases also can be utilized for SAR studies. These databases have been reviewed comprehensively in a recently published paper

[10]. With these information resources, the quality as well as the quantity of SAR can be improved and increased. Additionally, the phenomenal development of new computer software and hardware that can be applied to SAR studies is on the market almost monthly. All of these ingredients (information base, novel hardware, and software) should make it possible for notable advancements to be made in the use of SAR in the field of toxicology.

Even though the information base and technology for the efficient conduct of SAR studies have improved, those engaged in regulating chemicals must realize that there is not an easy or a completely effective method for predicting toxicological activity from chemical structure. The best and most efficient method still remains the "gut reaction" of a person knowledgeable in both a given area of toxicology and chemistry. Federal agencies responsible for the regulation of chemicals and exposure to toxic substances have (to our knowledge) no standard agency-wide method, procedure, or technique for the systematic study of SAR. Because of the lack of a sufficiently validated method or procedure, application of SAR in the evaluation of chemical risks or chemical hazard assessments varies and the contribution of SAR to the process of chemical hazard assessment is not fully realized. The SAR studies that are performed among federal agencies usually are approached through liberal use of intuitive and deductive reasoning by responsible staff, much to the credit of the individual practitioners of this procedure. Although it will never be practical to separate human reasoning from SAR practices, reliance on these "gut reactions" cannot be the primary method of choice. Federal agencies need a plan for SAR implementation that makes more efficient use of available tools or resources that can be applied appropriately to the planning and implementation of SAR studies. Currently, most of the methods and models proposed for SAR work are either too complicated, theoretical, or costly for practical use in the day-to-day efforts to assess chemical hazards or risks. Furthermore, total reliance on machine predictions via computer models, artificial intelligence programs, or neural networks should be used only in the process of categorizing chemicals for further study and assessment. Note that most of these models and approaches have not been validated thoroughly. To date, the more promising of the SAR methods are those that capitalize on the human element when making inferences regarding the role that chemical structure plays in initiating a toxic effect.

3.2. Discussion of issues regarding the quality and quantity of information

Once the problem of how to access the primary toxicology literature has been resolved, the next question is, "How reliable are the data reported in this literature?" To determine this, users of the information must rely on their own personal knowledge and the editorial policy standards of the published source. One of the most thorough and large-scale reviews of the toxicology literature occurred during 1979. This review was part of the EPA's Gene-Tox Program and provided an interesting look at the quality of the literature being published in one specific area of toxicology. Most journals failed to maintain a strict editorial policy with respect to format; data presentation; and the inclusion or referencing of key or essential information elements regarding such obviously vital items as specific details of agent(s) tested, control data,

experimental design, and protocol used. Because of these deficiencies, only 52% of the papers reviewed were used in Gene-Tox; it is indeed interesting that almost half of the literature was not used. Some of the papers were not used because they were either written in a foreign language, not published in a refereed source, or did not contain original data. The majority, however, did not meet the rigid criteria established by the various Gene-Tox review panels. The criteria used by Gene-Tox may be found in the various published panel reports for each bioassay. The number of papers used varied with each panel and bioassay. For example, the Chinese hamster ovary (CHO) cell gene mutation panel used only 8% of the papers screened [11]. Since the initial publication of the criteria for the CHO assay, however, better than 75% of the papers reviewed have been used.

The increase in the number of papers used for the Gene-Tox exercise followed an appeal to authors and journal editorial boards by Gene-Tox participants. Primarily because of the Gene-Tox Program's review of the 1960–1979 literature and subsequent recommendations on assay protocols and data reporting, the percentage of literature published during the 1980–1988 era used by Gene-Tox to update results from the 1980–1988 literature for several selected assays increased noticeably. The literature used during the update phases of the Gene-Tox review was 75 to 90% as compared with the dismal showing of 8 to 52% used from the 1969–1979 literature. Some journals, such as *Mutation Research*, made adjustments in their editorial policies to ensure the inclusion of key information in manuscripts submitted for publication.

4. Conclusion

There are several information resources that can be of immense help in assessing the risks of chemical exposure to human health and the environment. The challenge to contemporary chemical regulatory toxicology practitioners is knowing or being familiar with those resources that offer the best source of information to apply to a specific question, issue, or problem.

As we look to the challenges of the future, more information will be generated and developed regarding the adverse health effects of chemicals. Toxicity data, human health data, and other information obtained from many different types of biological systems will become available. If this information is to be used properly, it will be necessary to know which files or databases offer the best access to the literature. Furthermore, along with this awareness studies devoted to examining, identifying, and correlating biological activity patterns with human health protection should come. Work to accomplish this must become a standard part of the risk assessment process. Knowing the best means to acquire needed information for review and analysis has become an essential requirement for all toxicologists as well as for all scientists in general. With such a capability, for example, we may learn more about the animal models being used or proposed to study the toxic effects of chemicals and their applicability to human hazard assessment. Furthermore, by having ready access to the toxicology literature, the capability to study patterns in biological test data will be

possible and will provide the ability to investigate the exceptions that may be found in the data. In doing so, it will be possible to focus on the more crucial experiments needed to determine the validity of a particular model to the risk assessment process before investing too heavily in a particular model or test system. More importantly, ready access to the toxicology literature can also increase our knowledge of the underlying processes or causative factors responsible for initiating a specific type of toxicological event.

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