Life Sciences 145 (2016) 284–293

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Health effects of toxicants: Online knowledge support

Philip Wexler [a,*], Richard Judson [b], Sally de Marcellus [c], Joop de Knecht [c], Eeva Leinala [c]

[a] National Library of Medicine (NLM), Toxicology and Environmental Health Information Program, USA
[b] Environmental Protection Agency (EPA), USA
[c] Organisation for Economic Co-operation and Development (OECD), Environment Directorate, Environment, Health and Safety Division, France

ARTICLE INFO

Article history:
Received 21 August 2015
Received in revised form 26 September 2015
Accepted 2 October 2015
Available online 24 October 2015

Keywords:
Toxicology
Computerized information
Databases
Toxicity
Environmental health
Toxicoinformatics
National Library of Medicine
US Environmental Protection Agency
OECD
Toxicology information
Chemical databases
Hazardous chemicals
Toxicology information
Toxicology databases
Environmental health database
Online toxicology information
Online toxicology resources

ABSTRACT

Research in toxicology generates vast quantities of data which reside on the Web and are subsequently appropriated and utilized to support further research. This data includes a broad spectrum of information about chemical, biological and radiological agents which can affect health, the nature of the effects, treatment, regulatory measures, and more. Information is structured in a variety of formats, including traditional databases, portals, prediction models, and decision making support tools. Online resources are created and housed by a variety of institutions, including libraries and government agencies. This paper focuses on three such institutions and the tools they offer to the public: the National Library of Medicine (NLM) and its Toxicology and Environmental Health Information Program, the United States Environmental Protection Agency (EPA), and the Organisation for Economic Co-operation and Development (OECD). Reference is also made to other relevant organizations.

Published by Elsevier Inc.

1. Introduction

Scientific research relies upon and contributes to an ever growing body of data and information, leading to subject specific knowledge frameworks which evolve over time. Historically, libraries have played a critical role as repositories of information (using the word in its broadest sense), and served as the primary access points for retrieval. Computerization, the advent of the Internet, and mobile devices have resulted in the digitization of virtually all forms of information, broken down geographic boundaries, and immeasurably aided in our ability to find whatever we are looking for, wherever we may be. Moreover, a vast amount of this is free. Some physical libraries have been at the forefront of innovating digital information tools but other organizations not traditionally in the business of information provision have also become adept at making large data sets available globally online at no cost to the user. The field of toxicology is just one scientific discipline that has benefited enormously from the electronic dissemination of information. This paper will highlight electronic information available from three major suppliers of toxicity data — a US biomedical library, a US environmental regulatory agency, and a multi-lateral governmental forum headquartered in Europe, each of which has consolidated and linked various resources in portal-like products. It will also take a brief look at a handful of the many other worldwide online tools which can assist in the pursuit of toxicity data.

2. NLM and TEHIP

A component of the US National Institutes of Health (NIH), the National Library of Medicine (NLM), founded in 1836 and currently located in the Washington DC suburbs, is the world's largest biomedical library. Its Toxicology and Environmental Health Information Program (TEHIP) has been a leader and focal point for information related to health and other aspects of environmental toxicants since its inception in 1967 as the Toxicology Information Program. It was created in response to recommendations of the President's Science Advisory Committee (PSAC). The Committee's report (PSAC, 1966, Handling of Toxicological Information,

* Corresponding author.

http://dx.doi.org/10.1016/j.lfs.2015.10.002
0024-3205/Published by Elsevier Inc.

Washington, DC, White House) concluded 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 must be more generally available to all those legitimately needing such information."

Today, nearly 50 years later, in first quarter of the 21st century, TEHIP continues to meet the needs of toxicologists and the public through state-of-the art databases and other online tools. One can link to these resources through the Program's home page at sis.nlm.nih.gov/enviro.html. Most of its databases of relevance to environmental toxicants, and the subject of this paper, are accessible through its TOXNET (Toxicology Data Network) system at toxnet.nlm.nih.gov. TOXNET houses a cluster of databases covering an extensive array of information on potentially hazardous chemicals, and their health and environmental effects. It offers user-friendly searching and features such as relevancy ranking, flexible sorting, and downloading options. It is free online and publicly accessible worldwide. A number of TOXNET databases, briefly reviewed below, are also available for leasing.

2.1. ChemIDplus (http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp)

Chemical identification is often a key starting point to learning more about a chemical's properties and toxicity. TOXNET's ChemID*plus* is a dictionary of over 400,000 chemicals. Chemical preferred names and synonyms, CAS Registry Numbers, molecular formulas and weights, and 3-D structures are included within the records. For any given chemical, there are many links to other NLM databases, to resources external to NLM (such as from the EPA, NIOSH, the OECD) and to federal and state regulatory lists on which the chemical might appear.

2.2. HSDB (Hazardous Substances Data Bank) (http://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm)

HSDB presents an across the board view of over 5600 potentially hazardous chemicals and their properties. While most often consulted for its substantial toxicity data, it is an excellent source for a myriad of other information, including:

- Human health effects
- Emergency medical treatment
- Animal toxicity studies
- Metabolism/pharmacokinetics
- Pharmacology
- Environmental fate & exposure
- Environmental standards & regulations
- Chemical/physical properties
- Chemical safety & handling
- Occupational exposure standards
- Manufacturing/use information
- Laboratory methods
- Special references
- Synonyms and identifiers
- Administrative information.

Each of the above broad categories of information is actually divided into more precise data fields. For example, the human health effects category contains the following fields: toxicity summary, evidence for carcinogenicity, human toxicity excerpts, skin, eye and respiratory irritations, drug warnings, medical surveillance, populations at special risk, probable routes of human exposure, body burden, average daily intake, reported fatal dose, and milk concentrations. Further classifications are also available for some fields. The study summaries presented within human toxicity excerpts, for instance, may be categorized by a variety of sub-fields such as human exposure studies, signs and symptoms, case reports, epidemiology studies, surveillance, biomonitoring, genotoxicity, alternative and in vitro tests and endocrine modulation. Data in the non-human toxicity excerpts field is also classified by a number of sub-fields.

An NLM Chemical Selection Team is responsible for choosing chemicals for inclusion based upon factors such as degree of toxicity, level of exposure and production volume. Chemicals of interest to various US government agencies, regulatory and otherwise, as well as global organizations, are other sources used to locate candidate chemicals. Finally, chemicals which are newsworthy for a positive (e.g. the newest wonder drug) or negative (e.g. massive chemical spill) reason also receive priority consideration. Data are drawn from a core set of monographs, government documents, technical reports, and the primary journal literature. A distinguishing characteristic of HSDB is the peer-review process used to build it. Its Scientific Review Panel (SRP), a committee of 16 scientists with expertise cutting across the database's major subject areas, meets 3 times a year to review, add, edit, and update its chemical records, some 300 per meeting. Associated with each data statement in HSDB is one of three data quality tags, as follows:

- Peer reviewed — for data statements which have been peer reviewed by the SRP;
- QC reviewed — for data statements which have received a preliminary quality control review, but not yet been reviewed by the SRP;
- Unreviewed — for a limited number of data statements, such as industry submissions, which do not readily lend themselves to scientific review but which may contain useful information nonetheless.

HSDB continues to be enhanced with new information and features. In recent years, for example, there has been an increased effort made to include more data on radionuclides, nanoparticles, reptile, scorpion, and spider venoms, plant toxins, and antivenins. Newer generation pesticides are being included as are EPA "green" chemicals, and chemical warfare agents are being updated. Visual displays will accompany text where appropriate. These may include, for example, metabolic pathways, pictograms used in the Globally Harmonized System of Classification and Labeling of Chemicals (GHS), and graphics representing venomous or poisonous animals, and poisonous plants. An ecotoxicity data element has also been created with subheadings for birds and mammals, aquatic species, other terrestrial species, field studies, and accidental poisonings. Consumer summaries will be added to provide succinct and easy to understand information summarizing toxicity and other characteristics of HSDB chemicals.

2.3. TOXLINE (Toxicology Literature Online) (http://toxnet.nlm.nih.gov/newtoxnet/toxline.htm)

In library terminology, a bibliography is a list of works about a particular subject. These days, bibliographies include references to both printed and digital sources. TOXLINE is a bibliographic database containing citations to literature covering the biochemical, pharmacological, physiological, and toxicological effects of chemicals, including drugs. The majority of TOXLINE's citations include abstracts, indexing terms, and CAS (Chemical Abstracts Service) registry numbers. Updated weekly, TOXLINE's more than 4 million references date from as early as the 1840s to the present.

TOXLINE is derived from a number of sub-files, with the largest portion coming from NLM's PubMed/MEDLINE database. Complementing this is literature from the DART (Developmental and Reproductive Toxicology) database and technical reports from Federal Research in Progress (FEDRIP), Toxic Substances Control Act Test Submissions (TSCATS), Toxicology Document and Data Depository (NTIS), and Toxicology Research Projects (NIH Reporter). DART, funded by serval agencies, is also searchable as a free-standing database of more than 200,000 journal references on teratology and other aspects of developmental and reproductive toxicology. Rounding out TOXLINE are 13 archival collections which, despite no longer being updated, still contain valuable references. Among these are the International Labor Office,

International Pharmaceutical Abstracts, Pesticides Abstracts, Poisonous Plants Bibliography, Swedish National Chemicals Inspectorate, etc. Citations from TOXLINE can be imported into reference management programs such as EndNote. Advanced searching allows users to specify particular fields and to limit retrieval to certain years, language or subfiles.

2.4. Additional NLM databases

Many other specialized databases of relevance to the health effects of toxic agents are available through the TOXNET system and elsewhere within TEHIP and NLM.

The Household Products Database (http://householdproducts.nlm.nih.gov/) links a multitude of consumer products to health effects on Material Safety Data Sheets provided by manufacturers. In addition to ingredient and manufacturer information, the Database lists acute and chronic health effects of chemical ingredients in specific brands and includes links to information in other NLM databases.

Worker health and safety information is highlighted in Haz-Map (http://hazmap.nlm.nih.gov/), an occupational health database with information on the adverse effects of workplace exposures to chemical and biological agents. A variety of links are between chemicals, diseases, industries, jobs, particular job tasks and processes, and non-occupational activities such as arts and crafts. Exposure limits are included as well.

NLM also offers several databases which focus on drugs and herbals, and their effects. The Drug Information Portal (http://druginfo.nlm.nih.gov/drugportal/), in addition to providing brief drug descriptions, serves as an entrée to an array of summary drug information, including toxicity, from other NLM and NIH databases. DailyMed (http://dailymed.nlm.nih.gov/dailymed/) includes FDA approved labels, also referred to as medication package inserts, while Pillbox combines images of pills and other information to allow users to visually search for and identify oral solid dosage form medications. A collaboration between the NIH Office of Dietary Supplements and NLM gave rise to the Dietary Supplement Label Database (DSLD) (http://dsld.nlm.nih.gov/dsld/). It contains the full label information from a sample of dietary supplement products marketed in the U.S. This includes product information, suggested usage, dosage, and ingredients, label statements including precautions, if available, and contact information. LactMed (Drugs and Lactation Database) (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm) provides information on drugs and other substances to which breast feeding mothers may be exposed. It includes information on levels in breast milk and infant blood, and possible adverse effects in the nursing infant, as well as suggested therapeutic alternatives, if advised. LiverTox (http://livertox.nih.gov/), prepared by NLM in concert with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) provides unbiased information on drug induced liver injury caused by prescription and nonprescription drugs, herbals and dietary supplements.

Risk assessment is addressed by the Integrated Risk Information System (IRIS) (http://toxnet.nlm.nih.gov/newtoxnet/iris.htm) and International Toxicity Estimates for Risk (ITER) (http://toxnet.nlm.nih.gov/newtoxnet/iter.htm), both databases with a high level of peer review. IRIS is a database developed and maintained by the EPA (see below), which highlights data in support of human health risk assessments, including hazard identification and dose–response assessments. Both cancer and non-cancer effects via oral and inhalation routes are accounted for. Meanwhile, ITER is compiled by Toxicology Excellence for Risk Assessment Center (TERA), part of the Department of Environmental Health at the University of Cincinnati's College of Medicine. ITER includes IRIS data and enhances it with data from other international groups including the Agency for Toxic Substances & Disease Registry (ATSDR), Health Canada, the Dutch National Institute for Public Health and the Environment (RIVM) and others. Presented in a tabular format, ITER allows for easy comparison between risks derived by these groups, displaying values such as ATSDR's minimal risk levels, Health Canada's tolerable intakes/concentrations and tumorigenic doses/concentrations, and EPA's carcinogen classifications, unit risks, slope factors, oral reference doses and inhalation references concentrations.

The Comparative Toxicogenomics Database (CTD) (http://toxnet.nlm.nih.gov/newtoxnet/ctd.htm) contains manually curated data describing cross-species chemical–gene–disease relationships. The results provide insight into the molecular mechanisms underlying variable susceptibility and environmentally influenced diseases.

Several archived but still relevant databases are: the Chemical Carcinogenesis Research Information System (CCRIS) (http://toxnet.nlm.nih.gov/newtoxnet/ccris.htm), the Carcinogenic Potency Database (CPDB) (http://toxnet.nlm.nih.gov/newtoxnet/cpdb.htm), and the Genetic Toxicology Data Bank (GENE-TOX) (http://toxnet.nlm.nih.gov/newtoxnet/genetox.htm).

2.5. More NLM tools relevant to toxicology

The Toxics Release Inventory (TRI) (http://toxnet.nlm.nih.gov/newtoxnet/tri.htm), containing data collected by the US EPA mandated by the Emergency Planning Community Right to Know Act of 1986, is a pollutant release and transfer registry listing numbers of pounds of certain chemicals released to the air, water, soil or via underground injections, plus off-site waste transfers, and source reduction and recycling data, as further stipulated by the Pollution Prevention Act of 1990. While not providing health effects data per se, records link to other NLM databases, such as HSDB, to provide toxicity information. TOXMAP (http://toxmap.nlm.nih.gov/toxmap/), a companion Geographic Information System utilizes maps as visualization tools for both the TRI and Superfund programs.

In addition to meeting the needs of the professional toxicologist, NLM also seeks to inform general audiences concerned about health effects of toxicants. While some of the above databases can serve both groups, TEHIP has also expressly developed products for users without a strong technical background. ToxLearn (http://toxlearn.nlm.nih.gov/) and ToxTutor (http://sis.nlm.nih.gov/enviro/toxtutor.html) are multimodular tutorials focused on the basics of toxicology at an undergraduate level. Its K-12 offerings include ToxMystery (http://toxmystery.nlm.nih.gov/), ToxTown (http://toxtown.nlm.nih.gov/), and the Environmental Health Student Portal (http://kidsenvirohealth.nlm.nih.gov/). Enviro-Health Links (http://sis.nlm.nih.gov/pathway.html) provides overviews which include links to scientifically reliable information, largely from government agencies on topics such as arsenic, mercury, climate change, outdoor air, pesticides, nanotechnology, etc. NLM's MedlinePlus (https://www.nlm.nih.gov/medlineplus/), designed for the consumer, includes sections on Drugs and Supplements, and Poisoning, Toxicology, Environmental Health.

Closely aligned with NLM's TEHIP is its Disaster Information Management Research Center (DIMRC) (http://disaster.nlm.nih.gov/dimrc/toolsnlmdimrc.html), a focal point for health information resources in the service of disaster preparedness, response, and recovery. Emergency response tools are available, for example, for dealing with chemicals (CHEMM) and radiation (REMM), while WISER is a system designed to help emergency responders identify hazardous materials and respond to chemical emergencies.

3. United States Environmental Protection Agency (EPA)

The United States Environmental Protection Agency (EPA) is charged with protecting human health and the environment, and uses high quality scientific information to make a variety of risk assessment and risk management decisions. The Agency both generates data in-house through its Office of Research and Development (ORD), and compiles other data from public and private sources such as the peer-reviewed literature and reports submitted by companies in support of new product registration requests. The EPA has major programs in air and radiation, chemical safety and pollution prevention, solid waste and emergency response, and water pollution prevention. A relatively new

focus area is computational toxicology which is using high-throughput in vitro assays and models to characterize thousands of chemicals at a time for both health and exposure metrics. Much of the data collected by EPA is made publically available in the form of web sites on single chemicals, downloadable files, and downloadable relational databases. In addition, the EPA has developed a large number of computer models that can be used to make predictions of chemical hazards. Here we highlight public data and models, focusing on hazard as opposed to exposure. However, some of the sites listed will contain information on both.

Below are described EPA's largest and most comprehensive databases of chemical structure, property and health-related information, and models related to these data domains. However, the EPA maintains a much larger collection of smaller and more specialized data sets and models. These are all indexed in the READ (Registry of EPA Applications, Models and Databases) system (http://ofmpub.epa.gov/sor_internet/registry/systmreg/home/overview/home.do). Currently there are 895 entries in READ, which can be accessed by navigating to the Search Info Resource link.

3.1. Large online databases

3.1.1. EPA Substance Registry Services (SRS) (http://ofmpub.epa.gov/sor_internet/registry/substreg/home/overview/home.do)

SRS is a system that indexes EPA-wide (and some non-EPA) information on chemicals. SRS does not contain data itself, but instead provides links to the primary sources of data. This includes information on chemical hazards as well as regulations governing the use of chemicals. In particular, SRS will note whether information on the chemical is contained in the EPA regulatory databases.

3.1.2. DSSTox (http://www2.epa.gov/chemical-research/toxcast-chemicals-data-management-and-quality-considerations-overview) Distributed Structure-Searchable Toxicity database)

DSSTox is a large collection of high-quality, curated chemical information of environmental and toxicological relevance. It was initially constructed to track chemicals specifically related to data sets used in modeling toxicology endpoints and to support the EPA's ToxCast program and the US inter-agency Tox21 Consortium. Subsequently, it branched out to include hundreds of thousands of chemical structures In particular, all chemicals in the ACToR system (see below) are being registered in DSSTox, which is replacing the chemical identity and structure portion of ACToR. Likewise, all of the other EPA ORD databases are transitioning to using DSSTox for chemical identity information. In the original version, each structure and its corresponding CASRN and name were largely hand-curated, while in the present version, more automated methods are being employed to allow the chemical inventory to grow substantially. However, as a service to users, all structures are classified based on the level of curation. In addition to chemical names, structures and CASRNs, DSSTox includes many lists of chemicals (e.g. chemicals subject to specific regulations) and chemical synonyms. A chemical-specific dashboard is being constructed to allow searching by name, CASRN and structure.

3.1.3. ACToR (http://actor.epa.gov) Aggregated Computational Toxicology Resource

ACToR is an EPA ORD warehouse of publicly available chemical toxicity data, aggregating information from over 2000 public sources. As mentioned above, chemical structure and name information is housed in the DSSTox database. Data in ACToR is organized by “data collections” (all chemicals and data from a particular source) and “assays”, which are specific data sets. An assay is organized as a rectangular array with rows representing chemicals and columns representing “assay components”. The entire ACToR data model is patterned after that of PubChem, an NIH/NLM database providing information on the biological activities of small molecules. Data can take a variety of simple forms, including numeric or textual, or consist of URL links to external data sites. Data is not curated beyond what is provided by the original sources, although data sets are updated periodically to keep in synchrony with the source data site. All assays are organized in terms of an assay category taxonomy. The top level categories related to health are Inherent Chemical Property (physico-chemical properties), Exposure (exposure information for humans and ecological species), Occurrence (e.g. biomonitoring data), Risk Management (e.g. safe exposure levels), and Hazard (specific toxicological information). One interesting extension of ACToR is the CPCat database (Chemical and Product Categories, http://actor.epa.gov/cpcat) which summarizes data from ACToR regarding how chemicals are used in consumer and industrial products. This is key information for building exposure models. All of the information in ACToR, DSSTox and the other EPA NCCT (National Center for Computational Toxicology) databases are being made available through RESTful web services at http://actorws.epa.gov/actorws.

3.1.4. ToxRefDB (http://www2.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data) Toxicity Reference Database

ToxRefDB is a compilation of guideline or guideline-like in vivo animal data from tests run on pesticide active ingredients and other chemicals. Data is collected at the dose-group level (as opposed to the individual animal level), and lists all treatment-related effects seen for each dose group. Currently, all critical effects (as determined in setting the Lowest Observable Adverse Effect Level or LOAEL), are being added to the databases, as are individual animal counts for the critical effects. This will allow the calculation of benchmark dose (BMD) levels and other points of departure (PODs). Summary data from National Toxicology Program (NTP) guideline studies is also included in ToxRefDB. Currently, ToxRefDB is available through ACToR, and as a large data file download from the URL provided above.

3.1.5. ToxCast dashboard (http://actor.epa.gov/dashboard2)

This is the first of a collection of dashboards being developed by the EPA NCCT to provide targeted access to specific data collections, models or risk assessment tools. Specifically, this dashboard provides access to data from the NCCT high-throughput screening (HTS) program called ToxCast. This program has generated HTS data on thousands of chemicals of toxicological interest in up to 700 assay endpoints in concentration response. The dashboard provides visual displays of the concentration-response profiles and curve-fitting parameters. Chemical information is provided by DSSTox.

3.1.6. EDSP21 dashboard (http://actor.epa.gov/edsp21)

This is an example of an EPA NCCT risk assessment dashboard, supporting the EPA's Endocrine Disruptor Screening Program (EDSP). The EDSP is mandated to test approximately 10,000 chemicals for their ability to disrupt endocrine signaling via the estrogen, androgen and thyroid signaling pathways. The EDSP21 dashboard currently allows access to estrogen and androgen receptor (ER and AR) in vitro assay data on about 1800 chemicals and ER QSAR (Quantitative Structure-Activity Relationship) model and literature data on a larger fraction of the EDSP universe. Also included are exposure estimates for the EPA ExpoCast program. As more EDSP-related information becomes available, it will become visible through this dashboard.

3.1.7. ECOTOX (http://cfpub.epa.gov/ecotox)

This is the world's largest database of information on toxicology information on chemicals in aquatic life, terrestrial plants, and terrestrial wildlife. Information is primarily curated from the peer-reviewed literature. The database provides online queries by chemical, species and effects, and also provides downloads of the entire database. It is continuously updated. Priorities for adding chemicals are determined by EPA, but are typically driven by the needs of EPA regulatory offices.

3.1.8. EPA IRIS (http://www2.epa.gov/iris)

EPA's Integrated Risk Information System compiles extensive reports on the toxicology of more than 550 high-profile chemicals. The resulting points of departure (PODs, e.g. reference doses/RfD, reference concentrations/RfC) and other quantitative values are used as definitive acceptable exposure levels by EPA, states and many other national and international organizations. The IRIS database is web accessible, with the information contained in a collection of searchable documents that describe the health effects of individual substances and that contain descriptive and quantitative information for cancer (oral slope factors, oral and inhalation unit risks) and non-cancer (RfD, RfC) effects. IRIS is developed and maintained by the EPA National Center for Environmental Assessment (NCEA). IRIS is also available via NLM's TOXNET system as described earlier.

3.1.9. EPA ChemView (http://java.epa.gov/chemview)

This is a portal for information on industrial chemicals regulated by the EPA Office of Pollution Prevention and Toxics (OPPT) under the Toxic Substances Control Act (TSCA). This includes information submitted by companies to the EPA as well as information on EPA assessments (e.g. IRIS) of the chemicals. Data can be quantitative and tabular, or can link to another site. Data for one chemical and one endpoint class at a time can be downloaded.

3.1.10. EPA HPVIS (http://cfub.epa.gov/hpv-s/)

The EPA High Production Volume Information System, HPVIS, complements ChemView, and contains significant amounts of quantitative toxicology information on chemicals regulated under TSCA. Data types are physico-chemical properties, fate and transport, ecotoxicology and mammalian toxicology. HPVIS is limited to "high-production volume" chemicals, i.e. those manufactured or imported at levels of 1 million pounds a year or more. The current database contains information on about 900 chemicals. Although there is no ability to download the entire database, customized queries can be built that allow for export of large amounts of tabular data.

3.2. Online model collections

3.2.1. TEST (http://www2.epa.gov/chemical-research/toxicity-estimation-software-tool-test) Toxicity Estimation Software Tool

TEST is a downloadable Java-based application developed to estimate a variety of toxicity and physical property endpoints. TEST utilizes a consensus-based approach in which the prediction is made by averaging the predictions from several different QSAR methods including hierarchical clustering and group contribution based methods. The QSAR models were developed using a pool of more than 800 two-dimensional descriptors. Predictions from each QSAR methodology are subject to a series of constraints which ensure each predicted value represents an interpolated value rather than an extrapolated one. TEST includes models for a variety of toxicity endpoints including acute aquatic toxicity, acute mammalian toxicity, and mutagenicity. TEST also has a variety of physical property estimators including melting point, boiling, flash point, viscosity, and thermal conductivity.

3.2.2. UberTool (http://qed.epa.gov/ubertool)

This tool is collecting a large number of spreadsheet-based ecotoxicology models used by the EPA and migrating them to a web-accessible format. The initial focus has been on models that are used in the context of performing risk assessments for endangered species. Specific models are divided into the terrestrial and aquatic categories. Some tools have specific uses in the context of either pesticide or industrial chemical risk assessments.

3.2.3. Web-ICE (http://www3.epa.gov/ceampubl/fchain/webice/) Web-based Interspecies Correlation Estimation

Web-ICE is an internet based ecotoxicity extrapolation tool developed to estimate acute toxicity (LC50/LD50) of a chemical to a species, genus, or family from the known toxicity of the chemical to a surrogate species. The extrapolation models are least square regressions of the relationship between surrogate and predicted taxa acute toxicity values. Web-ICE has modules to predict acute toxicity to algae, aquatic animals (amphibians, fish and invertebrates), and wildlife (birds and mammals) for use in ecological hazard and risk assessments. The tool also contains modules that generate Species Sensitivity Distributions (SSDs) from Web-ICE generated data, and for predicting toxicity to U.S. threatened and endangered species. The tool is used within EPA and the international risk assessment community in estimating toxicity to taxa with limited data, including endangered species, and for augmenting the species diversity of SSDs.

4. Organisation for Economic Co-operation and Development (OECD)

The Organisation for Economic Co-operation and Development (OECD), established in 1961 and headquartered in Paris, has as its mission the promotion of policies to improve the economic and social well-being of people around the world. Since 1978, the OECD's Chemicals Programme, has helped its member governments (currently numbering 34) develop and implement high-quality chemicals management policies and instruments to support assessing and managing the risks of chemicals. Now, in the digital era, this includes the development and promotion of corresponding Information Technology (IT) systems in order to achieve significant efficiencies.

To harmonize the way electronic information on the properties of chemicals is structured and exchanged, the OECD develops harmonized standards, the "OECD Harmonised Templates" (OHTs), a guide for structuring data when reporting summaries of chemical test results (http://www.oecd.org/ehs/templates). The data elements contained in each template comply with the reporting requirements of the OECD Test Guidelines as well as other national/international methods used for the study of chemical properties relevant for chemical safety assessments. As such, these templates facilitate circulation of data used in regulatory assessments of chemicals through meta-analysis and cross-check, while avoiding duplication.

The following five systems make a large body of toxicity data and information, as well as means to predict missing toxicity data, accessible on-line at no cost to the user.

4.1. The eChemPortal, the global portal to information on chemical substances (http://www.oecd.org/ehs/echemportal)

The eChemPortal, the Global Portal to Information on Chemical Substances, was established in 2007 to support chemical safety decisions by regulators and other stakeholders (industry, academics, international organizations and the general public). eChemPortal facilitates access to information via direct links to multiple Web sites containing collections of chemical hazard, risk, exposure and use information, and harmonized/reviewed Globally Harmonized System of Classification and Labeling of Chemicals (GHS) classifications, prepared for national, regional, and international chemical review programs. eChemPortal, currently hosted by the European Chemicals Agency (ECHA), can be found at http://www.oecd.org/ehs/eChemPortal.

Currently there are twenty-nine participating data sources from Australia, Canada, Finland, France, Germany, Japan (e.g. Japan CHEmicals Collaborative Knowledge database [J-CHECK]), New Zealand, the United Kingdom, the United States (e.g. High Production Volume Information System [HPVIS]), the European Union (e.g. ECHA Dissemination Portal), and other international organizations. eChemPortal provides descriptions of the sources and review of data stored in these participating

data sources. Static links are also provided to scheduling information of national/regional and international assessments.

The three main functionalities of eChemPortal, the search by chemical substance identity, the search by properties and effects, and the search by GHS classification are directly accessible from the homepage.

- Substance search
  The search by chemical identity has two search fields:
  - The number field (e.g. Chemical Abstracts Service Registry Number, or European Commission Number), is the most precise way to find results for a specific chemical.
  - The chemical name field allows searches by chemical names as well as by synonyms, trade names and names in languages other than English and permits searches by partial names via the use of an asterisk as a wildcard symbol.

- Property search
  The search by property screen displays a list of 68 endpoints for physical and chemical properties, environmental fate and pathways, ecotoxicology, and toxicology. For example, 22 endpoints are listed for the following toxicological information:
  - Toxicokinetics, metabolism and distribution
  - Acute toxicity
  - Irritation/corrosion
  - Sensitization
  - Repeated dose toxicity
  - Genetic toxicity
  - Toxicity to reproduction
  - Specific investigations: neurotoxicity and immunotoxicity.

The structure of the property data stored in eChemPortal allowing these searches is based on the OECD Harmonised templates.

- GHS search
  A new search by classifications according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) was released in June 2015. This search allows users to view, for an individual chemical, GHS classifications which have undergone review by a regulatory body or intergovernmental organization.

Once the search has been performed and links retrieved, users can follow the links to access the full information in the participating data sources. Links to all data sources can be found via the Substance Search. Currently, four data sources participate (submit data to be found via) the Property Search and two data sources participate via the GHS search. The number of data sources participating in eChemPortal is continuously increasing.

4.2. OECD existing chemicals database

The OECD Existing Chemicals Database, accessed at http://www.oecd.org/env/hazard/data, contains the assessments of the OECD Cooperative Chemicals Assessment Programme (CoCAP) and associated documents. The CoCAP produced OECD-wide agreed upon hazard assessments mostly of existing industrial High Production Volume (HPV) chemicals. An assessment is made from a reference dataset, the OECD Screening Information Data Set (SIDS), compiled from available information. The SIDS covers the following information:

- Chemical identity: CAS number, name, structural formula, composition
- Quantity produced
- Use pattern
- Physico-chemical properties: physical state, melting & boiling points, vapor pressure, water solubility, dissociation constant, partition coefficient between water and octanol
- Environmental fate: photodegradation, stability in water, transport and distribution between environmental compartments, ready biodegradability
- Environmental toxicology: acute toxicity to fish and invertebrates, growth inhibition in aquatic plants, chronic toxicity only when this is more relevant than acute data
- Mammalian toxicology: acute toxicity by most relevant route of exposure, repeated dose toxicity, genetic toxicity in vitro, reproductive toxicity, developmental toxicity.

An assessment contains: i) an assessment report discussing the key findings for each hazard endpoint covered in the assessment, ii) a profile summarizing the conclusions for each hazard endpoint, and iii) study summaries or robust study summaries for data gathered on each hazard endpoint covered in the assessment. The chemical assessment can cover all SIDS endpoints or a sub-set of SIDS endpoints (i.e. targeted assessment), with the addition of non-SIDS endpoints occasionally. Some robust study summaries were elaborated with the International Uniform Chemical Information Database (IUCLID) system and are available for download in IUCLID export file format (structured data according to the OECD Harmonised Templates). The database provides a functionality to search for the assessment by e.g. name and CAS number of the chemical, sponsor and type of assessment (targeted/non-targeted).

4.3. OECD QSAR Toolbox (http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm)

OECD has developed an IT tool to predict the properties of chemicals: the OECD QSAR Toolbox. The OECD QSAR Toolbox contains a wide collection of scientific information, data with results from experimental studies and models, together with scientific procedures that allow users to predict the properties of a chemical based on the experimental evidence available for similar chemicals. The toolbox enables profiling chemicals according to their chemical structure or specific mode of action in order to define criteria for grouping them with similar chemicals into categories. As a next step the toolbox can predict missing experimental values by read-across and trend analysis from tested to untested chemicals within a category and/or by (Q)SAR (quantitative structure-activity relationship) models.

Within the Toolbox, structural alerts provide a basis for forming toxicologically relevant categories. The more useful profilers implemented in the toolbox are those based on extended structural fragments associated with chemical reactivity, such as profilers for covalent chemical reactivity with DNA and proteins. Moreover, additional mechanistic and endpoint-specific profilers were developed and implemented into the Toolbox. The principles of structure-activity focus on building relations between molecular structures and physical, chemical and biological properties of chemicals. A major pitfall in the development and implementation of these structure-activity relationships is correct presentation of chemical structures. Some chemicals at test or field conditions as a result of chemical, photochemical or biologically mediated transformations are altered and the observed effect(s) are a result of quite different chemical structures compared to the original substance. Among the most important chemical processes altering the chemical structure are hydrolysis, dissociation and tautomerism. Simulators of these processes were implemented in the Toolbox to improve the formation of chemical categories. Useful interpretation of metabolic and abiotic fate of chemicals has been improved by the addition of several metabolic simulators which aid in identifying the formation of reactive intermediates or persistent end products. An advanced search module has also been implemented to allow for the construction of logically combined search blocks thus giving the ability to perform flexible queries in the databases of the Toolbox.

Because of the complexity and variety of knowledge implemented in the Toolbox, much effort has been made to streamline the operations and to make the software more intuitive and user-friendly. These efforts include help functions, guidance documents and training aids. The Toolbox can import and export data files according to the OECD

Harmonised Templates and hence facilitate the exchange of data with other systems compatible with OECD Harmonised Templates, most notably IUCLID.

After the release of version 3.0 in 2012, several updates of the existing functionalities and databases and several new databases and profilers have been implemented, e.g. a metabolism simulator based on observed rat in vivo metabolism, structural alerts associated with respiratory sensitisation, a QSAR model for predicting the phototoxic potential of chemicals and a framework for identifying chemicals with structural features associated with the potential to act as developmental or reproductive toxicants developed by Procter & Gamble, and databases on metabolism rates in fish from Environment Canada. The latest version (3.3.5) was released in July 2015 and can be downloaded from the following web site: http://www.qsartoolbox.org.

The success of the current version of the Toolbox has led to the formulation of Phase 3 and a chance to further address the long-term issues associated with the prediction of complex hazard endpoints. Specifically, the major areas for Phase 3 development are; (i) usability improvement, (ii) scientific development, including use of mechanistic knowledge to group chemicals, (iii) development of additional functionalities, (iv) general improvements related to enhancements of IT technology, and (v) corrective system maintenance.

4.4. AOP knowledge base

To facilitate the development of the predictive approaches outlined above and to promote their regulatory use, OECD has launched a program for the development of adverse outcome pathways (AOPs) to improve the mechanistic understanding of how chemicals interact with living organisms. As a tool to support this program, the OECD together with other stakeholders is contributing to the development of the AOP Knowledge Base [accessible at https://aopkb.org], which assembles several platforms. One is the AOP Wiki, where information on AOP is collected largely in a qualitative, narrative way. Another tool in development is Effectopedia [an alpha version is accessible at www.effectopedia.org], where AOPs are implemented in a computable way.

4.5. OECD substitution and alternatives assessment toolbox (OECD SAAToolbox)

The OECD Substitution and Alternatives Assessment Toolbox (SAAToolbox) is a compilation of resources related to chemical substitution and alternatives assessments and can be accessed at the following website: http://www.oecdsaatoolbox.org/. Bringing together this information contributes to the goal of advancing tools and approaches to support decision making for the substitution of chemicals of concern.

The OECD SAAToolbox was released in January 2015 and serves as a repository and access point for tools to aid those looking for further information regarding the field or those wanting to conduct an assessment of a chemical alternative or substitute.

The toolbox is divided into four different sections:

- Alternatives assessment tool selector;
- Alternatives assessment frameworks;
- Case studies and other resources;
- Regulations and restrictions.

The alternative assessment tool selector is focused on hazard assessment and enables users to search for tools that would best serve their particular purpose by filtering them by key attributes of interest to the user. Some examples of the attributes included are the type of chemical hazard attributes (human health, ecotoxicity, etc.), other comparative attributes (cost/benefit analysis, exposure, life-cycle impacts etc.) and whether the tool has guidance available or has a fee associated with. This segment of the OECD SAAToolbox describes, and can be used to compare, each of the individual tools. It also provides links to other tools of interest in other domains such as exposure, cost/benefits and availability, life-cycle impacts, and materials management.

The section on alternative assessment frameworks describes and links to various frameworks and guidance documents that have been developed for the conduct of alternatives assessment and substitution, while the case studies section helps in accessing specific case examples, toolkits and product rating systems from government and non-governmental organizations, industry, and academia. Finally the regulations and restrictions section provides access to lists of chemicals that have been regulated or restricted in jurisdictions or by industry sectors, as well as non-governmental organization lists.

5. Last but not least

In addition to the three agencies highlighted above, there are numerous other government agencies, serving regulatory and research purposes, trade associations, professional societies, independent research organizations, and non-governmental organizations (NGOs) which provide public access to toxicological information. Several of these are highlighted below:

5.1. The Agency for Toxic Substances and Disease Registry (ATSDR)

ATSDR is a US federal public health agency within the Department of Health and Human Services charged with implementing the health-related sections of laws protecting the public from hazardous wastes. As such, its functions include public health assessments of waste sites, health consultations concerning specific hazardous substances, health surveillance and registries, and response to emergency release of hazardous substances.

ATSDR offers a number of information resources relevant to toxic substances and useful for toxicological and health professionals, community members, emergency responders, and health care providers. In particular, their *Toxicological Profiles* (http://www.atsdr.cdc.gov/toxprofiles/index.asp) are peer reviewed documents extensively cataloging toxicity and adverse health effects information on chemicals. The *Public Health Statements* (http://www.atsdr.cdc.gov/PHS/Index.asp), provide succinct summaries of the Toxicological Profiles and are drawn from the first chapter of the latter. An even shorter and less technical account is provided by ATSDR's *ToxFAQs*(*http://www.atsdr.cdc.gov/PHS/Index.asp*).

In addition, ATSDR generates minimal risk levels (MRLs) for priority hazardous substances. These are based upon the most sensitive non-cancer health endpoints consistent with a list of priority health conditions (PHCs). Their Medical Management Guidelines (http://www.atsdr.cdc.gov/mmg/index.asp) were developed as an aid to emergency department physicians and other emergency healthcare professionals who manage acute exposures resulting from chemical incidents. A number of Medical Education and Training tools are also available through the ATSDR's site, e.g. Case Studies in Environmental Medicine, Ground Rounds in Environmental Medicine, and Toxicology Curriculum for Communities Trainer's Manual.

Links on ATSDR's Toxic Substances Portal (http://www.atsdr.cdc.gov/substances/index.asp) allow users to access information by health effect, chemical classification, particular chemical or geographically by community for which a Public Health Assessment, or Health Consultation, was conducted.

5.2. National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP)

NIEHS is a component of the US National Institutes of Health (NIH), part of the Department of Health and Human Services. NIEHS focuses its resources on the environmental causes of disease. Its monthly peer reviewed journal, *Environmental Health Perspectives* (http://ehp.niehs.nih.gov/), is among the highest impact factor ranked journals in areas related to environmental health and toxicology. NIEHS also offers an array of online databases and information tools (http://www.niehs.

nih.gov/research/resources/databases/index.cfm). These include Chemical Effects in Biological Systems (CEBS), Drug Matrix, Micoarray Center cDNA Clone Search, Nanomaterial Registry, and ToxFX, an automated toxicogenomics analysis application.

NIEHS is also home to the National Toxicology Program (NTP) an interagency program (comprised of NIEHS itself, the National Institute of Occupational Safety and Health (NIOSH), affiliated with CDC, and the National Center for Toxicological Research (NCTR), affiliated with the FDA) dedicated to testing and evaluating environmental chemicals. NTP's goals include providing toxicological evaluations on substances of public health concern, developing and validating improved toxicology methods, strengthening the scientific basis of risk assessment, and communication to stakeholders. NTP issues the *Report on Carcinogens* (http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html), a report mandated by the US Congress that identifies substances or exposure circumstances that may cause cancer in humans. Substances are tagged as either *known* or *reasonably anticipated* human carcinogens.

5.3. Food and Drug Administration (FDA) and National Center for Toxicological Research (NCTR)

The US FDA (http://www.fda.gov) is responsible for assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, the food supply, cosmetics, and products that emit radiation, including the regulation of tobacco products.

Among FDA's many databases:

- Recalls, market withdrawals, and safety alerts (food)
- Outbreak investigations (food)
- FDA adverse event reporting system (FAERS) quarterly data files (drugs)
- MedWatch: the FDA safety information and adverse event reporting program
- Drug trials snapshot (drugs).

The National Center for Toxicological Research (NCTR) (http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm) is an FDA research component intent on developing a scientifically sound basis for regulatory decisions and reducing risks associated with FDA-regulated products. NCTR offers a group of Bioinformatics tools relevant to toxicity information, among them ArrayTrack, atBioNet, Estrogenic Activity Database, Liver Toxicity Knowledge Base (LTK) and SNPTrack.

Note also that *Foodsafety.gov* (http://www.foodsafety.gov) is a US government site integrating food safety information from the FDA and the US Department of Agriculture.

5.4. Occupational safety and health

The Occupational Safety and Health Administration (OSHA) (https://www.osha.gov), a US regulatory agency and part of the Department of Labor, is responsible for assuring safe and healthful occupational settings for the workplace population. The Mine Safety and health Administration (http://www.msha.gov) exists in parallel to prevent death, disease, and injury from mining and to promote safe and healthful workplaces for miners. Hazardous chemicals represent but one among many risks to miners and other workers.

The National Institute for Occupational Safety and Health (NIOSH) (http://www.cdc.gov/niosh), within the US Centers for Disease Control is, in a sense, the research counterpart to the above agencies. Their databases include the NIOSH Pocket Guide to Chemical Hazards, the Emergency Response Safety and Health Database, and the NIOSH Chemical Agent Information for Emergency Responders.

The Encyclopedia of Occupational Health and Safety (4th edition) and the CISILO database, two important occupational safety and health resources, are searchable (http://www.ilocis.org/en/cis_srch.html) via the Canadian Centre for Occupational Health and Safety (CCOHS) (http://www.ccohs.ca), which also offers CHEMINDEX, a chemical dictionary of over 200,000 chemical names and CAS RNs.

5.5. European Chemicals Agency

The European Chemicals Agency (ECHA) (http://echa.europa.eu), founded in 2007 in Helsinki, is responsible for implementing the European Union's chemicals legislation, REACH, for the protection of human health and the environment. They have a number of databases relevant to chemicals manufactured and imported in the European Union, covering hazardous properties, registration and evaluation of substances, classification and labeling, information on safe use and a database relevant to chemicals subject to prior informed consent (PIC).

5.6. World Health Organization (WHO) & International Programme on Chemical Safety (IPCS)

WHO's IPCS (http://www.who.int/ipcs/en/) works to establish the scientific basis for the sound management of chemicals, and to strengthen national capabilities and capacities for chemical safety. IPCS issues several series of publications. A an example, within the Assessment series on health impacts of chemicals, their Environmental Health Criteria monographs (http://www.inchem.org/pages/ehc.html), offer extensive data on a wide range of chemicals and chemical classes. They examine physical and chemical properties, analytical methods, sources of exposure and environmental transport, chemobiokinetics and metabolism, effects on animals, and an evaluation of risks for human health and the effects on the environment.

Other IPCS online documents of relevance include the Concise International Chemical Assessment Documents, Health and Safety Guides, International Chemical Safety Cards, Joint Meeting on Pesticide Residues Monographs and Evaluations (JMPR) and Joint Expert Committee on Food Additives Monographs and Evaluations (JECFA), the latter two produced jointly by WHO/FAO Expert Committees.

5.7. International Agency for Research on Cancer (IARC)

IARC (http://www.iarc.fr/) is another specialized agency of the WHO, and devoted to promoting international collaboration in cancer research. In the toxicological realm, one of their major publications is the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. These Monographs identify environmental factors that can increase the risk of human cancer. In addition to individual chemicals, they cover complex mixtures, occupational exposures, physical and biological agents, and lifestyle factors. Interdisciplinary working groups of expert scientists review the published studies and evaluate the weight of the evidence that an agent can increase the risk of cancer. Since 1971, more than 900 agents have been evaluated, of which more than 400 have been identified as carcinogenic, probably carcinogenic, or possibly carcinogenic to humans.

5.8. And that's not all

The above listing represents a number of resources of merit in the field of toxicology informatics. The assemblage is not comprehensive. For example, many other national governments provide on-line information regarding their chemical management programs, and these resources often provide access to toxicological information. Examining links available on many of these sites and spending some time with a search engine such as Google will yield additional electronic resources, including databases, relevant to the health effects of toxicants.

6. Challenges

While a surfeit of information is often considered a good thing, one sometimes needs to step back and consider the broader implications

and challenges of such abundance. As each database or tool is developed for a specific purpose, with specific users in mind, there are risks for duplication of effort and creation of information silos. As databases are designed, developers need to actively consider the opportunity to harness information that others have already curated, to complement it, instead of increasing duplication, and to consider how information can be shared. The OECD has been tackling these transnational issues with the development of the eChemPortal (linking to data sources in more than 10 jurisdictions) and with the development of more than 100 OECD harmonized templates. These templates have as a basis a common mark-up language (XML) that facilitates the electronic exchange of data across different computer systems for data entry, storage and management. These templates are increasingly used as the basis for information systems in regulatory programs in OECD countries, however further efforts are needed to harmonize, not only among jurisdictions, but also among industrial sectors. This will help to better identify information gaps, lead to re-use of data and will ultimately provide users of toxicological information the benefit of the most complete set of public information.

An additional challenge is that toxicological information is published in multiple languages. Automated translation, especially for technical subjects, is at best approximate. Human translation, although resource and time intensive, is the obvious means to overcoming the linguistic barrier. As a first step, further efforts could be made to translate summaries of information. For example, the Japan Existing Chemical Data Base (http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp) makes available the toxicity test reports from Japan's existing chemicals safety program, including data summaries in English, while individual study reports are available in Japanese.

Another approach to addressing language issues as well as to improve networking and coordination of toxicological activities globally is the World Library of Toxicology, Chemical Safety, and Environmental Health (WLT) (http://wltox.org), a component of the Toxipedia group of resources (http://toxipedia.org). Launched in 2009 at the Seventh Congress of Toxicology in Developing Countries (CTDC-VII) in Sun. City, South Africa, the WLT is a multilingual online portal of links to key global resources, representing a host of individual countries and multilateral organizations. The Site is designed as a network of, and gateway to, toxicological information and activities from around the world. It is built on a Wiki platform by a roster of Country Correspondents, with the aim of efficiently exchanging information and stimulating collaboration among colleagues, and building capacity, with the ultimate objective of serving as a tool to help improve global public health.

More work can also be done in conveying to the public the importance of toxicology and environmental health to people's everyday lives. Toxipedia itself, a free online toxicology encyclopedia, is seeks to meet the need of offering understandable toxicology information to the public. Meanwhile, the Toxicology Education Foundation (TEF) (http://toxedfoundation.org) is devoted to encouraging, supporting, and promoting educational activities that increase the public understanding of toxicology. Its Web site offers a multitude of links, videos, and other resources.

ecause the countries generating the greatest amount of toxicological data are free market economies, trade secrets are generally respected. This stimulates competition and preserves intellectual property rights but, of course, at the cost of open public access. Holders of proprietary information should continue to be encouraged to make as much data available to public databases as feasible. This will increase the comprehensiveness of toxicological information for all users.

7. Conclusions

Toxicology benefits from an extensive online information infrastructure. Databases and tools for a variety of audiences ranging from the public to the professional toxicologist are widespread. As with any topic, the Internet can yield questionably reliable information, however, there remains a great deal that is scientifically sound, highly credible, and authoritative. This paper aims to help users sort through this information and provides three exemplary entry points from long established organizations known and respected for tailoring their information to the multiplicity of needs of toxicologists and others in the toxicological community — the National Library of Medicine, the US Environmental Protection Agency, and the Organisation for Economic Co-operation and Development. Information sources such as TOXLINE, the Hazardous Substances Data Bank, ACToR, and eChemPortal are among the sturdiest foundational elements supporting online knowledge about toxicants and their health effects. NIEHS/NTP, ATSDR, FDA, OSHA, IARC, ECHA, and WHO are examples of other institutions which contribute to the global framework of toxicology information and whose online information sources are also highly worthy of consideration. Additional digital information resources not even touched upon in this review originate in many areas of the developed and developing world beyond North America and Europe, via government, academic, non-profit, and commercial sectors. While toxicological information is ample and widespread, often peer reviewed and of high quality, challenges, though relatively minimal, do exist. Data duplication and gaps, the need for better coordination, language differences, and limits to access of proprietary information are, to a reasonable extent, being addressed presently.

Disclaimer

The opinions expressed and arguments employed herein are those of the authors and do not necessarily reflect the official views of the OECD or of the governments of its member countries.

Acknowledgment

This paper was supported by the Intramural Research Program of the National Institutes of Health, National Library of Medicine.

A Reading list

[1] Committee to Review the IRIS Process, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council, Review of EPA's Integrated Risk Information System (IRIS) Process, National Academies Press (US), Washington (DC), Jun 25 2014 (http://www.ncbi.nlm.nih.gov/books/NBK230072/).
[2] G.C. Fonger, et al., The National Library of Medicine's (NLM) hazardous substances data bank (HSDB): background, recent enhancements and future plans, Toxicology 325 (Nov 5 2014) 209–216.
[3] S. Fowler, J.G. Schnall, TOXNET: information on toxicology and environmental health, Am. J. Nurs. 114 (2) (Feb 2014) 61–63.
[4] C. Hochstein, et al., Ten years of change: National Library of Medicine TOXMAP gets a new look, Med. Ref. Serv. Q. 33 (4) (2014) 428–437.
[5] R. Judson, et al., ACToR—aggregated computational toxicology resource, Toxicol. Appl. Pharmacol. 233 (1) (2008 Nov 15) 7–13.
[6] R.S. Judson, et al., Aggregating data for computational toxicology applications: the U.S. Environmental Protection Agency (EPA) aggregated computational toxicology resource (ACToR) system Int, J. Mol. Sci 13 (2) (2012) 1805–1831.
[7] R. Kavlock, et al., Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management, Chem. Res. Toxicol. 25 (7) (2012) 1287–1302.
[8] S. de Marcellus, eChemPortal — the global portal to information on chemical substances, in: P. Wexler (Ed.), Encyclopedia of toxicology, 3rd ed., 3, Academic Press, Elsevier Inc 2014, pp. 655–662.
[9] M.T. Martin, et al., Profiling the reproductive toxicity of chemicals from multigeneration studies in the toxicity reference database, Toxicol. Sci. 110 (1) (2009) 181–190.
[10] OECD, Cutting costs in chemicals management: how OECD helps governments and industry, OECD Publishing, Paris. (2010). http://dx.doi.org/10.1787/9789264085930-en.
[11] OECD, The Environment, Health and Safety *Programme*: 2013–16, (Brochure), OECD, Paris, 2013 (http://www.oecd.org/env/ehs/Environment-Health-Safety-Brochure.pdf).
[12] OECD, Current Landscape of Alternatives Assessment Practice: A Meta-Review, Series on Risk Management No. 26″ (report). OECD, Paris, 2013 http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2013)24&doclanguage=en).
[13] S. Raimondo, et al., Web-based Interspecies Correlation Estimation (Web-ICE) for Acute Toxicity: User Manual. Version 3.1. EPA/600/R-12/603, Office of Research and Development, U. S. Environmental Protection Agency, Gulf Breeze, FL, 2013

[14] A.M. Richard, et al., Chemical structure indexing of toxicity data on the internet: moving toward a flat world, Curr. Opin. Drug Discov. Dev. 9 (3) (2006) 314–325.
[15] P. Tomasulo, ITER — international toxicity estimates for risk, new TOXNET database, Med. Ref. Serv. Q. 24 (1) (2005) 55–66 (Spring).
[16] P. Tomasulo, LactMed-new NLM database on drugs and lactation, Med. Ref. Serv. Q. 26 (1) (2007) 51–58 (Spring).
[17] P. Wexler, Information Resources in Toxicology, 4th ed. Elsevier/Academic Press, 2009.
[18] P. Wexler, The U.S. National Library of Medicine's toxicology and environmental health information program, Toxicology 198 (1–3) (May 20 2004) 161–168.
[19] P. Wexler, et al., The world library of toxicology, chemical safety, and environmental health (WLT), Hum. Exp. Toxicol. 31 (3) (2012) 207–214.
[20] A. Wullenweber, et al., Resources for global risk assessment: the international toxicity estimates for risk (ITER) and risk information exchange (RiskIE) databases, Toxicol. Appl. Pharmacol. 233 (1) (Nov 15 2008) 45–53.