

Education for Toxicologists Via Internet

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Abstract

Background and purpose: The Internet offers a wide range of online digital resources for the field of Toxicology.

Methods: The history of toxicology and electronic data collections are reviewed. This review presents a brief and non-comprehensive overview of a representative sampling of some of the broad array of toxicology-related learning, tutorial and information resources now becoming widely available to educators, health professionals, students and the general public via the Internet.

Results: A broad variety of useful learning and reference resources in the general fields of toxicology and the environmental health sciences is provided to introduce the reader to the diverse types of information currently available. Distance education and educational media resources are also available online in the field of toxicology. As molecular biology and computational tools improve, new areas within toxicology such as structural activity relationship analysis, mutational spectra databases and toxicogenomics, now have resources online as well.

Conclusion: The sources and Internet links contained in this review will hopefully constitute a useful resource of basic toxicology information that should be readily accessible to most if not all Iranian readers.

Keywords: TOXICOLOGY; ENVIRONMENTAL HEALTH SCIENCES; EDUCATION; TUTORIALS; INTERNET

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Introduction

The Internet has been used as an educational delivery medium for distance education classes, as a repository for educational material and as a medium of exchange of ideas. The relatively recent explosive growth of the Internet and wide availability of powerful and affordable personal computers in our country has vastly increased Iranian access to an impressive array of digital information sources, including many that offer important toxicological and environmental

health information. New resources previously toxicology and biological sciences, and thus assist them in making rational decisions regarding everyday activities and lifestyle choices.

Methods

Numerous sites are readily available to provide easy access to accurate, practical and useful health-related information in language readily understood by the lay population. The Wellness site at University of California Davis serves as but a single good example of this type of reliable health-related information [<http://wellness.ucdavis.edu/>] that has become widely accessible.

However, although the Internet has made available to the general public these vast amounts of readily accessible information, it unfortunately provides access to both reliable and unreliable

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information. Since the Internet generally lacks any form of peer-review process, essentially anyone may post any information they wish and purport it to be factual, whether it is of sound scientific basis or merely supportive of personal, political or social agendas, or based upon well-intentioned albeit false or misleading information. Thus the public is faced with the daunting challenge of assessing the veracity of the information with which they are presented. Regrettably, a vast amount of inaccurate and even outright false information is now readily available to the layperson and professional alike and has proliferated at seemingly the same rate as the overall explosive growth of the Internet itself. Several illustrative examples of the various guises in which the extremes of such misinformation may occur can be found at the following web sites: [<http://www.urbanlegends.com/>], [<http://www.ulrc.com.au/>], [<http://www.snopes.com/>]. These commercially maintained Internet sites serve as repositories and archives of some of the more outlandish examples of scientific and toxicological misinformation (often sprinkled with snippets of accurate information) currently available in the public domain.

While entertaining, as well as alarming, sites such as those noted above nonetheless provide a graphic perspective of the magnitude of the challenge for the average person in distinguishing between accurate and inaccurate information on the Internet. Children and young adults in particular have difficulties ascertaining which sites are reliable and are providing accurate information, and are even more likely than adults to accept everything they find on the Internet as valid information. Thus, it is more important than ever that the public develop at least a rudimentary understanding of the basics of modern hypothesis-driven science and an elementary understanding of the basic concepts of toxicology. For representative examples of reliable basic toxicology information, visit: [<http://www.iet.msu.edu/journalists/citizen/citizen.htm>], [<http://www.sciences.com/layperson/default.htm>], [<http://www.uoguelph.ca/cntc/educat/guide/study.shtml>], [<http://www.bio.hw.ac.uk/edintox/page1.htm>].

Understanding such fundamental concepts in toxicology are essential for students and the public to comprehend and critically evaluate the large body of environmental health and toxicology-related information now readily available to them.

The scope of digital toxicology information, tutorials, and education available to the public is extensive, and this review should not be viewed as comprehensive. Rather, the author's intent is to provide the reader with a sampling of the various types of digital toxicology educational materials available on the Internet. Due to the ephemeral characteristics of web sites and the transitory nature of many educational programs, the examples for this review have in-part been selected as representative of educational efforts by well-established organizations such as governmental or educational institutions. The author offers his apology in advance to the many authors of additional excellent web sites and digital resources that exist but could not be included herein due to space limitations, as well as to the reader for links to Internet sites discussed herein that may become outdated.

Potential users and needs of digital information

The users of the digital information can be subdivided into four groups, each with somewhat different needs, sources of information and language preferences. The scientists naturally use all possible sources available. The Internet is a basic tool and international digital information sources are replacing textbooks for quick retrieval of information.

The Web is important to governmental and other authorities responsible for the safety of chemicals, drugs, food, drinking water, environmental health issues and occupational health. Much communication between experts occurs by e-mail.

The third, and a very important group, are municipal authorities responsible at a grass roots level, for the health of their citizens. At present the main responsibility for enforcing the legislation lies with municipal authorities. This group may potentially benefit the most from

digital information in the future, provided the appropriate information is available. Preferably it should be brief and in summary form, at a rather general level, in their native language Farsi and most importantly, relevant to their own country, Iran. The local authorities themselves increasingly produce and place information on the Web about local sources of exposures and the risks for their citizens.

The fourth, ever-increasing group, are the lay people. Most families have access to the Internet, at home, work or in a public library. They benefit from the same information as the municipal authorities but for them, the most important information are likely addresses for further contacts and 'what to do next'-type practical information. Some institutes have already prepared these kinds of Web pages. Such Web pages decrease the need for contacts by phone to answer simple questions.

Results

Although the tutorials, case studies, and ready-made toxicology curricula described above are extremely useful, the most accurate, detailed, and up-to-date information on toxicology and environmental health is still found in the primary research literature generated by these disciplines. For better or worse, the Internet now provides the general public with instantaneous and virtually no-cost access to the primary literature of the biomedical sciences, including toxicology.

Digital and internet-based toxicology learning resources

The National Library of Medicine (NLM) web site [<http://www.nlm.nih.gov/nlmhome.html>] provides worldwide public access to the primary literature in the biomedical and toxicological sciences. Although not directly targeted at toxicology information resources per se, the University of Buffalo offers a unique site that provides links to a very useful collection of tutorials to teach students, laypersons, and even professionals on how to search biomedical and toxicology related databases and develop useful search strategies to locate the information they desire [<http://ublib.buffalo.edu/libraries/units/hsl/>

[ref/tutorials.html#MEDLINE](http://www.nlm.nih.gov/pubs/web_based.html)]. These serve as useful supplements to the primary training manuals provided by the NLM itself [http://www.nlm.nih.gov/pubs/web_based.html], as well as the NLM sponsored 'Online Training Center' [<http://www.nlm.nih.gov/mar/online/index.html>] for searching the primary databases of biomedical and toxicology information (Medline, Toxline, etc.) using the standard NLM search engines such as 'Internet Grateful Med' [<http://igm.nlm.nih.gov/>] and 'PubMed' [<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>].

Of perhaps more direct relevance to the focus of this review, the Specialized Information Services (SIS) page of the NLM site [<http://sis.nlm.nih.gov/index.cfm>], provides an excellent gateway to a variety of toxicology and environmental health information resources and tutorials. The SIS site also provides direct access to searchable Toxicology [<http://sis.nlm.nih.gov/ToxSearch.cfm>], [<http://sis.nlm.nih.gov/tehip.cfm>] Chemical [<http://chem.sis.nlm.nih.gov/chemindex.html>], and Environmental Health [<http://sis.nlm.nih.gov/hotlines/>], [<http://sis.nlm.nih.gov/tehip.cfm>] databases, as well as brief descriptions of the content of these useful databases [http://sis.nlm.nih.gov/tox_chart.cfm]. Particularly valuable is a series of three outstanding 'Toxicology Tutorials' developed by the Toxicology and Environmental Health Information Program at NLM [<http://sis.nlm.nih.gov/toxtutor.cfm>]. These well-written tutorials, targeted toward the college undergraduate student, provide an excellent introduction to the basic concepts of toxicology. However, these highly recommended toxicology tutorials are sufficiently broad in their scope as to be useful to high school level students as well as more advanced students and professionals wishing to learn the basic tenets of toxicology. Moreover, they provide a sound basis for understanding the essentials of toxicology necessary to appreciate the research literature. The first of the three modules in the 'Toxicology Tutor' curriculum covers Basic Concepts in Toxicology, including an introductory overview and history, basics of dose-response

relationships, as well as introductory information on toxicity, organ system toxicity, toxic interactions, toxicology testing methodology, risk assessment and regulatory issues [<http://sis.nlm.nih.gov/toxtutor1/index.htm>]. The second of the three 'Tutor' modules addresses the basics of toxicokinetics. This tutorial consists of four sub-modules, each of which addresses one of the four key components of toxicokinetics; absorption, distribution, metabolism and excretion of xenobiotics [<http://sis.nlm.nih.gov/toxtutor2/index.htm>]. The third of the three 'Tutor' modules provides a summary of key concepts in cellular toxicology, with the goal of presenting and explaining basic concepts of cellular toxicology that operate at the biochemical and molecular level. Sections on the mechanisms by which xenobiotics perturb the basic physiology and biochemistry of cells are presented to explain basic mechanisms and targets of xenobiotic-mediated toxicity. Together, these three 'Toxicology Tutorials' provide a well-integrated and comprehensive basis for understanding the key aspects of the science of toxicology [<http://sis.nlm.nih.gov/toxtutor3/index.htm>] and are highly recommended to the reader.

Another web site that deserves the attention of the reader is the 'EnviroHealth Link' (EHL) site produced by Maryland Public Television with support from the NIEHS [<http://www.mpt.org/learningworks/teachers/ehl/>]. This site hosts an online compendium of complete lesson plans developed by master teachers for the EHL summer institutes. The visitor to 'Classroom Central' will find complete, downloadable lessons organized under headings such as Cancer, Environmental Toxins, Lead Poisoning, Radiation, and Water. The site also includes a complete online case study for middle school students called 'The Case of the Mystery Malady'. This online lesson opens with the following teaser: *Greenville has another epidemic on its hands. The Health Department's working overtime. The Earth Watch team is tied up. We need a good detective like you to take on the Case of the Mystery Malady.* Although the layout and graphics of the site are simple, the pages are

well organized, informative, and engaging. This site constitutes a valuable toxicology learning resource for both students and teachers.

The NIEHS maintains an outstanding web site containing a wealth of information regarding environmental health sciences and toxicology [<http://www.niehs.nih.gov/>]. While much of the information contained at this site would be of interest to the health professional or research scientist, this site also contains a great deal of information suitable for the general public and children as well [<http://www.niehs.nih.gov/external/facts.htm>]. Particularly worthwhile in this regard are the sections of this site devoted to 'Teacher Support' [<http://www.niehs.nih.gov/external/teacher.htm>] and students, i.e. the 'Kids Page' [<http://www.niehs.nih.gov/kids/home.htm>]. The 'Teachers Support' pages contain an excellent listing of environmental health science and toxicology curricular and education materials and links to NIEHS Community Outreach Centers [<http://www.niehs.nih.gov/centers/coep/coepcver.htm>] as well as links to a compilation of toxicology and environmental health related curricular materials developed with NIEHS support: [<http://www.niehs.nih.gov/external/crcldmmtr.htm>], [<http://www.niehs.nih.gov/od/k-12/k12home.htm>]. These should be valuable resources to many educators. The 'Kids Pages' contain an excellent assortment of entertaining and educational toxicology related exercises for children, and an extensive series of links to many other related sites [<http://www.niehs.nih.gov/kids/links.htm>]. Spanish language versions of several of the key NIEHS 'Kids Pages' are also provided.

The Society of Toxicology (SOT) [<http://www.toxicology.org/>] and Toxicology Education Foundation [<http://www.toxicology.org/AboutSOT/about-tef-frame.html>] currently provide only a limited amount of educational and tutorial information on their web sites, however the Society is currently in the process of dramatically expanding the educational materials to be posted on this site [<http://www.toxicology.org/Education/edu.html>]. Over the next year, this site is likely to become a

valuable resource for educational materials and links to other useful toxicology related sites. Nonetheless, a number of pages currently at this site warrant mentioning. The SOT site provides access to a 'Resource Guide to Careers in Toxicology' [<http://www.toxicology.org/careers/career.html>] a series of pages providing a concise overview of the discipline of toxicology, information about careers in toxicology, and information about educational programs in the toxicological sciences. It even includes a useful compilation of academic and post-doctoral toxicology training programs and related toxicology web sites and links. The SOT site also provides access to a widely utilized on-line placement service for toxicology-related job opportunities which also include job market surveys reviewing the prospects and opportunities for employment in toxicology-related industries and a salary survey of scientists employed in toxicology-related positions. Similarly, the Chemical Industry Institute of Toxicology (CIIT) site [<http://www.ciit.org/>] provides information about toxicology training opportunities [<http://www.ciit.org/EDUCATION/edprog.html>] and an extensive listing of links to additional toxicology and environmental health related web sites [<http://www.ciit.org/WWW/biochem.html>]. The National Environmental Education & Training Foundation (NEETF) web site offers a similar wealth of basic toxicology and environmental health education information, as well as many useful links to other toxicology and environmental health related sites [<http://www.neetf.org/>], [<http://www.neetf.org/links/index.htm>].

The EXTension TOXicology NETwork (EXTOXNET) is a cooperative effort of University of California-Davis, Oregon State University, Michigan State University, Cornell University, and the University of Idaho. This consortium maintains a useful web site offering objective, science-based information about pesticides. These materials are for the most part written for non-experts in the field and should be of use to educators, professionals and laypersons [<http://ace.orst.edu/info/extoxnet/>]. The site provides helpful tutorials on basic

concepts in toxicology and pesticide chemistry and also access to a number of searchable toxicology and pesticide information databases as well as many useful links to additional toxicology related web pages [<http://ace.orst.edu/info/extoxnet/newsletters/ucd1999a/links.html>]. The Environmental Protection Agency (EPA) [<http://www.epa.gov/>] also maintains a web site containing a large number of environmental health and toxicology related resources and provides a broad array of fundamental information related to chemicals and their use, as well as hazards associated with chemicals and environmental contaminants. Several sections of the EPA site warrant special note. The Office of Pollution Prevention and Toxics Homepage [<http://www.epa.gov/opptintr/>] provides access to a large database of information regarding specific chemicals for the interested citizen. This homepage also gives the visitor access to regulatory information, chemical resources and databases, and reports and initiatives targeted toward topics of particular environmental and toxicological concern. Also included is a section designed especially for children [<http://www.epa.gov/opptintr/opptedu.htm>] featuring an educational section entitled 'Learn About Chemicals Around Your House' designed to assist younger children in identifying household chemicals and their risks [<http://www.epa.gov/opptintr/kids/hometour/index.htm>].

The EPA Office of Pesticide Programs also maintains an excellent web site presenting basic information on pesticides, their use and human and environmental health implications [<http://www.epa.gov/pesticides/>]. This site includes detailed information on specific pesticides and classes of pesticides, regulatory information, and links to many other sites relating to pesticide toxicology and environmental health. There is also a series of pages containing information designed specifically for children of all ages [<http://www.epa.gov/pesticides/kids.htm>] as well as links to the EPA Teachers' Environmental Education Center [<http://www.epa.gov/teachers/>] and the EPA Student Center [<http://www.epa.gov/region5/students/>]. The pages

developed by the EPA Office of Children's Health Protection (OCHP) offer an excellent compendium of information relating to children's health and environmental health and toxicology issues. These pages provide access to a large body of information relating to toxicological issues that specifically impact children, and highlight specific susceptibilities of children to environmental and toxicological challenges [<http://www.epa.gov/children/index.htm>].

The Centers for Disease Control and Prevention (CDC) maintains a web site [<http://www.cdc.gov/>] that contains an extensive body of health related information and links, however the pages maintained by the Agency for Toxic Substances and Disease Registry (ATSDR) that focus more narrowly on chemicals and toxicology [<http://www.atsdr.cdc.gov/>] are especially useful and contain extensive information regarding chemicals and health risks. These include a number of searchable databases on toxicology and chemicals and their health effects, as well as some chemical exposure case studies. The 'Frequently Asked Questions in Toxicology (ToxFaqs)' pages may be especially useful for quickly locating toxicology information pertaining to a wide variety of potentially hazardous chemicals [<http://www.atsdr.cdc.gov/toxfaq.html#alpha>]. The ATSDR pages devoted to parents, teachers and health providers [<http://www.atsdr.cdc.gov/child/>] are a very good source of basic facts about toxicology, chemicals, and environmental health risks of a broad nature, and provide a large number of learning exercises targeted specifically to children and laypersons. The US Department of Health and Human Services (HHS) publishes a large number of web pages with direct relevance to many issues of human health, toxicology and environmental health [<http://www.hhs.gov/>] that offer a wealth of information useful to the general public. Furthermore, the site provides a link to the 'HHS Pages for Kids' site [<http://www.hhs.gov/kids/>], which consists of an extensive compilation of links to websites containing health-related information developed specifically for children and teens. This includes some very helpful sites developed for children by the FDA [[\[www.fda.gov/oc/opacom/kids/default.htm\]\(http://www.fda.gov/oc/opacom/kids/default.htm\)\], National Cancer Institute \(NCI\) \[<http://cancernet.nci.nih.gov/ocdocs/kidshome.html>\], and National Institute on Drug Abuse \(NIDA\) \[<http://www.nida.nih.gov/goestoschool/nidag2s.html>\] as well as a large selection of pages developed by many other government agencies specifically for children \[<http://www.hhs.gov/families/kids.htm>\]. The FDA site \[<http://www.fda.gov/>\] contains pages and links that provide particularly useful information, notably amongst them the 'Medwatch' pages containing information on potential new adverse effects of drugs \[<http://www.fda.gov/medwatch/index.html>\] and links to 'Food Safety and Nutrition' sites \[<http://vm.cfsan.fda.gov/list.html>\] including information relating to foods developed via biotechnology and genetic engineering \[<http://vm.cfsan.fda.gov/lrd/biotechm.html>\]. An excellent example of the many types of valuable Internet sites designed to offer practical health- and toxicology-related information to the general public is maintained by The Food Allergy Network \[<http://www.foodallergy.org/>\]. The site provides important and useful information about common allergic reactions to foods and food components, and a specially developed series of pages targeted especially to children and focusing on how to recognize and cope with potentially dangerous food allergies \[<http://www.fankids.org/>\]. A similar series of Internet sites are offered by the Asthma and Allergy Foundation of America \[<http://www.aafa.org/index.cfm>\] and American Academy of Allergy, Asthma and Immunology \[<http://www.aaaai.org/>\], again with sections developed especially for children \[<http://www.aafa.org/kidsandteens/>\], \[\[http://www.aaaai.org/public/just4kids/tim_moby.stm\]\(http://www.aaaai.org/public/just4kids/tim_moby.stm\)\]. The American Association of Poison Control Centers \[<http://www.aapcc.org/>\] has similarly developed a series of web pages with practical and potentially life saving information on common poisoning events along with links and phone numbers to local poison control centers \[<http://www.aapcc.org/zipcode/zip.asp>\]. The information provided under 'Prevention Tips' \[<http://www.aapcc.org/preventi.htm>\], and](http://</p></div><div data-bbox=)

'Prevention and Education' [<http://www.aapcc.org/educatio.htm>] is likely to be valuable to both the general public and educators. As a final example of this type of website designed to offer ready access to practical environmental health related information to the general public are the pages designed by the US Consumer Products Safety Commission to communicate important safety and hazard information on a variety of consumer products [<http://www.cpsc.gov/>]. This site also includes Spanish language versions of some information, consumer product recall notices, as well as pages focusing on children and hazards and products unique to children.

Another continuing area of very practical toxicological concern to the general public, and one that is also often at best only poorly understood, is the science of risk assessment. Of particular interest is how public policy and exposure limits are determined, especially for chemicals to which the public are perceived to be commonly exposed. A number of governmental and commercial Internet sites are available to assist the general public, students and health professionals in understanding the basic elements of scientifically-based risk assessment procedures. Representative examples of such sites include but are not limited to: [<http://www.epa.gov/ncea/>], [<http://www.epa.gov/ord/>], [<http://www.riskworld.com/>] and [<http://www.epa.gov/ngispgm3/iris/>]. These sites also provide links to a number of other useful resources that address a wide variety of environmental health issues [<http://www.webdirectory.com/>], the basics of risk assessment, software tools employed for conducting risk assessment studies [<http://www.epa.gov/ngispgm3/iris/links.htm>], [<http://www.riskworld.com/websites/ws5me001.htm>], [<http://www.epa.gov/ord/otherlinks.htm>], [http://www.rff.org/misc_docs/risk_book.htm#top], [<http://www.rff.org/methods/risk.htm>] and professional organizations dealing with risk assessment activities, such as the Society for Risk Analysis [<http://www.sra.org/>], International Society of Exposure Analysis [www.iseaweb.org], and Society of

Environmental Toxicology and Chemistry [<http://www.setac.org/>]. Several useful 'News Groups' and mailing lists are likewise available for subscription with a focus on various aspects of risk assessment, management and risk assessment policy making [<http://www.riskworld.com/newsgrps/ng5ng001.htm>].
More about Medline

Beginning with exposure considerations and evidence of human disease, OEH professionals likely made earlier use than other specialties of the clinical indices at the National Library of Medicine (NLM's MEDLINE). This resource now contains 11 million citations (and often abstracts) from thousands of peer-reviewed biomedical publication issued since 1966, and is now available without cost. Given interest and practice, both professionals and patients can unearth case examples, experimental information, mechanistic explanations and risk calculations on virtually any health topic.

MEDLINE began as immense paper compendia, known as Index Medicus, requiring year by year manual searches at medical libraries. It later provided an online resource utilized only by specialized librarians and zealous clinicians. First popularly available through the PC-based program *Grateful Med* and online *Paper Chase*, access was purchased based on time in use and the volume of data received. These programs operated by translating queries from simplified user menus into the library's own specialized syntax and provided only citations.

Presently, the most common approach to this accumulated data is through the free PubMed search engine created by the NLM itself [<http://pubmed.gov>]. Another newer free search tool is the NLM *gateway* [<http://gateway.nlm.nih.gov/gw/Command>] which permits highly complex queries to Medline as well as non-bibliographic health information including abstracts, and listings of health organizations from NLM's DIRLINE database. The PubMed search process is iterative and interactive, allowing users to monitor and mold output as it emerges. Findings can be narrowed to year of publication, species of interest, human age groups, publication language and even the availability of an online

abstract. Boolean operators ('AND', 'OR' and 'NOT') may be used to combine query responses and thus permit more selective identification of pertinent references. It is this Boolean logic that made MEDLINE so useful to OEH professionals in evaluating potentially attributable disease. Most early searches were queries to find reported cases combining an occupational exposure AND a particular disease.

Technical nuances which enable successful Medline searches include utilizing the chemical's unique Chemical Abstracts (CAS) identifier and the NLM's formally designated phrases for specific diseases and processes. *Occupational Exposure*, *Occupational Diseases*, and *Environmental Exposure* are examples of standardized terms (known as *MESH terms* or Medical Subject Headings) used by the NLM to index published materials and are powerful tools for searchers.

The library indexing staff also categorizes specific shorthand concepts such as toxicity (to), poisoning (po), adverse effects (ae), etiology (et) and epidemiology (ep) in more subtle but useful delimiters called *subheadings*. It should be noted, though, that the PubMed interface also allows users to simply enter a free-text query and retrieve equally useful, if somewhat less specific, results.

Given the power and reach of the available data, many professionals choose to train specifically in optimum use of MEDLINE, and university medical libraries offer instructions at many levels of sophistication. There are also commercial secondary vendors of Medline data (e.g. Ovid Technologies <http://www.ovid.com>) which provide supplemental capabilities and menu tools to make the search process more apparent and simpler. Links and licenses to online whole-text copies of the original articles (not just citations or abstracts) for specific publications may also be included. Broad access to these programs is often purchased as a privilege for university faculty and members of professional societies. Other vendors (e.g. Silver Platter [http://](http://www.silverplatter.com)

www.silverplatter.com) provide not only friendlier menus, but offline access (via CD-ROM) to literature subsets for specific topics, including OEH.

Additional occupational and Environmental web resources

The NLM also houses other primarily non-clinical information, specifically aimed at toxicology. The Toxicology and Environmental Health Information Program (TEHIP) site offers TOXNET [<http://toxnet.nlm.nih.gov>] a resource including several extensive and useful databases. The most biomedically oriented of these is the Hazardous Substances Data Bank (HSDB), where chemical information including human and animal health effects, and mechanisms of toxic injury are presented in a systematic format. Environmental management and safety issues are also presented, including information about environmental releases and kinetics of chemical degradation.

Often, OEH professionals need access to regulatory information instead of scientific findings or ideas. This mundane and frustrating task has been simplified by increasingly sophisticated online tools offered by regulatory agencies. In the United States, pertinent bodies include Occupational Safety and Health and Mine Safety and Health Administrations (OSHA and MSHA, both in the Department of Labor), Department of Transportation (DOT), Environmental Protection Agency (EPA), and the Department of Agriculture. Internet users may find these resources most readily through the US federal government's own search aide: [<http://www.fedworld.gov>].

OSHA in particular has a rich resource of regulatory documentation. Its central website [<http://www.osha.gov>] links to all necessary legal documentation including the history of its interpretative positions as well as explanatory technical information for implementation of regulatory standards. Available materials are often combined by industry affected, and include educational materials for workers at risk from specific hazards. Even enforcement actions are searchable by topic, industry and date. OSHA is not a scientific but a regulatory agency. National

Institute for Occupational Safety and Health (NIOSH) a part of the Centers for Disease Control and Prevention (CDC) is a supplemental resource for issues relating to OEH. The NIOSH site [<http://www.cdc.gov/niosh>] provides information regarding *best practices* in specific occupational situations, and comprehensive advisory guidelines for certain occupational hazards. Proposed exposure limits (often different than the standards enforced by OSHA) are posted, as well as the whole text of certain on-site investigations of work places with unusual health concerns (Health Hazard Evaluations).

NIOSH also provides a specialized citation and scientific literature index to biomedical resources beyond those offered at NLM, including textbooks and non-peer-reviewed abstracts. NIOSHTIC-2 [<http://www.cdc.gov/niosh/nishtic-2.html>] is a source for all of the agency's own funded research. The Registry of Toxic Effects of Chemical Substances (RTECS), [<http://www.cdc.gov/niosh/rtecs.html>] is another NIOSH-produced data-search product and is far more comprehensive. It presently includes over 130 000 chemicals, and provides very brief citations to published reports of toxic effects in both humans and animals. Toxicity data focus on primary irritation and acute toxicity; mutagenic, reproductive and *tumorigenic* effects; and specific numeric toxicity values such as LD50, LC50, TDLo, and TClO. For each citation, bibliographic sources are listed, enabling the user to access the actual studies. RTECS is available via paid subscription from the National Technical Information Service [<http://grc.ntis.gov/rtecs.htm>] as well as through several commercial data providers (e.g. Silver Platter or the Canadian Centre for Occupational Safety and Health <http://www.ccohs.org>).

The EPA offers similar depth and complexity, combining OSHA-like enforcement guidance and NIOSH-like science to develop and defend its regulatory mission. That mission is much broader than the interests of OEH professionals, and usually reflects general issues of environmental pollution rather than human health in particular. In compliance with EPA regulations, several

additional databases are accessed through the NLM under the TEHIP program, including the Toxics Release Inventory (TRI) in the TOXNET system at [<http://toxnet.nlm.nih.gov>] or directly at EPA's site [<http://www.epa.gov/tri>]. TRI contains federally-required reports of selected chemicals released from industrial sites on an annual basis. Though challenging to use, this information is a necessary basis for exploration of possible environmental (non-occupational) disease concerns.

The TRI data are also available in an easily accessed format created by the advocacy organization, Environmental Defense. *scorecard* [<http://www.scorecard.org>] offers graphical disclosure of exposure information based on chemical identity, geographical zip code, disease concerns and clinical symptoms. Not only are data available on year-by-year released tonnage, but contact information for corporate and congressional offices are available, in non-technical language.

There are other useful online resources for assessment of geographic-based exposure risk. One is *enviroMapper* [<http://map3.epa.gov/enviromapper>],

a site managed by the EPA showing the presence of *superfund* regulated hazardous waste sites. Another is the National Cancer Institute's Atlas of Cancer Mortality [<http://www.nci.nih.gov/atlas>] where county-specific rates of dozens of specific neoplasms are mapped for specific demographic categories.

The Integrated Risk Information System (IRIS, on the TOXNET system at <http://toxnet.nlm.nih.gov>) is another EPA-authored database accessible through both EPA and NLM websites. Containing over 500 chemical agents, IRIS emphasizes minimal exposure thresholds for health concern. It adds new chemical records when consensus determinations for an overall safety threshold can be achieved.

Another agency charged with evaluation of health risks from environmental exposure is the Agency for Toxic Substances and Disease Registry (ATSDR, <http://www.atsdr.cdc.gov>). ATSDR implements the health-related sections

of the laws that protect the public from hazardous waste and environmental spills of hazardous substances. ATSDR has developed several electronic toxicology resources. One of these is HAZDAT (Hazardous Substance Release/Health Effects Database, <http://www.atsdr.cdc.gov/hazdat.html>) which lists the contents of hundreds of pollution point-sources, especially federally designated superfund waste sites.

ATSDR is also the source of Minimal Risk Levels (MRLs) for 286 chemical exposures [<http://www.atsdr.cdc.gov/mrls.html>]. Here it uses the no-observed-adverse-effectlevel/uncertainty factor (NOAEL/UF) in deriving exposure recommendations for hazardous substances. Recommendations are set below levels that, based on current information, might cause adverse health effects, even in those most sensitive to such substance-induced effects.

Another agency with a specific health and safety focus is the Department of Energy (DOE), with special concerns regarding ionizing radiation and the development of energy resources. Its health and safety site [<http://tis.eh.doe.gov>] represents a dynamic and frequently updated resource for safety policies, news events and administrative actions regarding environmental cleanup. In addition to resource text files and instructions, the DOE site houses topic-specific discussion groups on its pages. Once users register for more complex services, the DOE resource provides a customized portal to its content.

The EPA has specific oversight responsibility for evaluating and registering pesticides and their use, and has an instructive reference web resource for Pesticide Safety Programs [<http://www.epa.gov/pesticides/safety/index.htm>] where regulations, scientific studies, and even emergency exposure guidance are provided.

The Department of Transportation [<http://www.dot.gov>] now has its own minor role in the topic of human toxicology and exposure assessment. Substance abuse testing of transportation workers is an important regulatory issue, and a dominant concern to professionals in OEH. The best resource for clinicians involved in this highly regulated activity is a private site

called *Transportation Medicine* [<http://home.att.net/~NataH>].

The Howard Hughes Medical Institute is a US consortium of research facilities and granted researchers involved in health research. Safety aspects of this complex industry are addressed at the Institute's website, providing chemical reference materials (Laboratory Chemical Safety Summaries at [<http://www.hhmi.org/research/labsafe/overview.html>]) and free worker education videos on fundamentals of safety management [<http://www.hhmi.org/research/labsafe/training/videos.html>].

Another laboratory safety resource is provided by the Lawrence Livermore National Laboratory, a DOE national laboratory operated by the University of California, whose website offers the entire policy and procedure manual for this facility's sophisticated program (http://www.llnl.gov/es_and_h/esh-manual.html).

Structure Activity Relationship (SAR) analysis SAR analysis can be considered to be computational toxicology. SAR combines toxicology data, bioinformatics, and computational analysis to create expert computer systems that can predict biological or toxicological effects of a new compound. This is accomplished by identifying reactive chemical structures in the new molecule and then using either previously gathered information or using statistical algorithms developed from previously gathered information to predict an effect (1 and 2).

One early SAR program based on statistical algorithms was developed by Dr Herbert Rosenkranz, University of Pennsylvania and Dr Jilles Klopman, Case Western Reserve University. Their academic research lead into the formation in 1996 of MultiCase, Inc, Beachwood, OH. This company offers a variety of SAR software including CASETOX, TOXALERT and MULTICASE [<http://www.multicase.com>] that, with the appropriate databases, provide predictions of various toxicology endpoints including genotoxicity. Another early program based on statistical

algorithms, TOPKAT®, provides separate modules for Ames mutagenicity as well as a variety of other short-term toxicology endpoints [<http://www.accelrys.com/products/topkat/index.html>]. The Oncologic® SAR program, developed by Logichem, Inc. Boyertown, PA in cooperation with the EPA, predicts carcinogenic potential within specific classes of chemicals [<http://www.logichem.com>].

Both the FDA and EPA have established programs to evaluate and use SAR modeling and prediction. The mission of the Regulatory Research and Analysis Program within FDA CDER is to construct electronic databases for pre-clinical toxicology studies for pharmaceuticals and to develop structure activity relationship (SAR) software programs to provide reliable estimates of the potential toxicities of FDA-regulated chemicals [<http://www.fda.gov/cder/otr/rras2.htm#prog7>]. The EPA has a number of SAR programs including the use of SAR in the High Production Chemicals Challenge Program [<http://www.epa.gov/opptintr/chemrtk/sarfin11.htm>].

One forum for publication of articles related to SAR is 'SAR and QSAR in Environmental Research' published by Taylor and Francis Group, London, UK [<http://www.tandf.co.uk/journals/titles/1062936x.html>].

Online resources for education in genetic toxicology

One of the first web-based training class in genetic toxicology has been developed by the IAEMS through a grant from the NIEHS, Research Triangle Park, NC, USA. The tutorial course on the Rodent Erythrocyte Micronucleus Assay In Vivo is available on the web [<http://www.iaems.nl/mainNC.html>]. Courses on other standard genetic toxicology assays, including the bacterial reverse mutation assay, are in preparation. There are also online educational resources for teaching general concepts in toxicology. One example are the toxicology tutorials available from the Specialized Information Services branch of NLM [<http://sis.nlm.nih.gov/Tox/ToxTutor.html>].

There are a variety of lecture outlines and course notes in various areas of genetic toxicology

provided by university professors. One example is an introductory online tutorial in genetic toxicology presented by Dr David H. Evans, Department of Molecular Biology and Genetics, University of Guelph, Guelph, Ont., Canada. This course provides an overview of the field of genetic toxicology, basic concepts of DNA damage, DNA repair, the consequences of mutations, and how mutations are detected [<http://www.uoguelph.ca/mbgwww/courses/94200/Toxicology.html>]. Another example of an online course overview is the webpage on DNA repair developed by Dr Joel Huberman, Department of Cancer Genetics, Roswell Park Cancer Institute, Buffalo, NY [http://mcbio.roswellpark.org/RPN530/DNA_Repair/DNA_Repair.html]. Many laboratories and research programs have webpages that also contain instructional material to provide background information. A good example of this is the website on the p53 gene maintained by the Institut Curie, Paris, France [<http://perso.curie.fr/Thierry.Soussi/index.html>]. Large professional associations have developed extensive websites to support education within their sphere of influence. One example is the American Society for Microbiology that has developed an extensive online resource with digital images for teaching, curriculum guides, online reviews of teaching materials and websites [<http://www.micrpbelibrary.org>].

The Internet is also a resource for locating academic programs in genetic toxicology. Professional societies such as the Society of Toxicology provides listings of graduate programs in toxicology with programs specializing in genetic toxicology identified [<http://www.toxicology.org/PublicOutreach/CareerResources/careerprograms.html>].

Examples of university webpages providing information about graduate research in mutagenesis are provided by the University of Texas Medical Branch, Galveston, TX [<http://www2.utmb.edu/pmch/geToxicology.htm>] and the Center for Environmental Health, University of Victoria, Victoria, BC [<http://web.uvic.ca/ceh/>].

Mutational spectra databanks

As laboratory techniques in genetic toxicology

have improved over the years the focus of research has moved from the organism to the cell and finally to the molecule. Mutation assays using intact organisms or intact cells to investigate genetic damage generally use phenotypic change in a marker to infer mutation in the controlling gene. The ability to sequence specific gene sequences from recovered putative mutant cells now permit molecular confirmation that a mutant phenotype actually results from an altered, mutated DNA sequence. Different types of genotoxins can produce characteristic genetic lesions that can be identified through sequencing. Information can be gathered on the mechanism of action of a genotoxic chemical by looking at the spectrum of mutants produced by the chemical. Sequence analysis can help identify hotspots in a gene where a specific mutation may result in altered function of the corresponding protein. Germline mutations can result in heritable genetic diseases and somatic mutations may result in cancer. Gene sequence analysis can help in diagnosis and identifying the mutational basis of a disease. For these reasons a large number of mutation databases with associated software tools have been developed. These databases tend to be structured to serve distinct needs and research communities. Some databases are organized around a specific locus or disease such the p53 mutation database maintained by the Laboratoire de Genotoxicologie des Tumeurs, Institut Curie, Paris, France [<http://perso.curie.fr/Thierry.Soussi/>] or the p53 mutation database maintained by International Agency for Research on Cancer, Lyon, France [<http://www.iarc.fr/p53/Index.html>].

Other mutational databases have been developed to serve specific research communities. The Mammalian Gene Mutation Database, maintained by Center for Molecular Genetics and Toxicology at the University of Wales, Cardiff, Wales [<http://lisntweb.swan.ac.uk/cmgt/index.htm>], collects the sequences of mutagen-induced gene mutations in mammalian tissues. Users may submit mutant gene sequences or search the database for specific mutants. Search criteria include type of mutagen,

species or cell line, tissue, specific mutational event or author. Results include all matching mutational events with hypertext links to literature citations. This database is designed to complement the Human Gene Mutation Database maintained by the Institute of Medical Genetics, at the University of Wales [<http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html>].

An example of how mutational spectra analysis has become part of genetic toxicology can be seen with the development of transgenic rodents for mutagenicity research. In the field of genetic toxicology, one goal has been to develop an easy, quick and inexpensive in vivo gene mutation model. The use of bacteria and mammalian cells in culture with homogenized rodent liver to simulate mammalian metabolism has become, by default, an alternative to predicting mutagenesis in vivo. Development of the molecular tools to insert recoverable shuttle vectors with target and reporter genes into the genomic DNA of animals led to the development of transgenic rodents such as BigBlue™ mice (3 and 4). These types of animals can be used to measure genotoxicity of chemicals in various tissues by recovering bacteriophage lambda shuttle vectors containing mutated *lacI* or *cII* target genes. Target genes in recovered shuttle vectors can be sequenced to confirm the underlying molecular basis for the change to the mutant phenotype (5). As mutants are sequenced, the sequence of each mutant can be submitted to a shared database and then analyzed relative to the spectra of mutants produced by other known mutagens. One such database used by researchers with the BigBlue model was developed by Dr Johan de Boer at the University of Victoria, Victoria, BC [<http://eden.ceh.uvic.ca/bigblue.htm>]. Another site that maintains searchable mutant spectra databases, including the transgenic *lacI* gene, is maintained by Dr Neal Carriello at 'Neal's DNA Mutation Site', [<http://www.ibiblio.org/dnam/mainpage.html>].

Toxicogenomics

Development of cDNA microarray technology has provided a powerful tool for the study of gene sequence, structure and expression (6 and

7). Using current microarray technology and analytical software, the expression of thousands of genes can be monitored simultaneously in two biological samples of interest, and the expression patterns compared. Traditional toxicology studies usually have relied on measuring the presence of an altered cell type that takes time to develop. For example, if the endpoint is a specific type of cancer, the process may take months or years to give a detectable tumor following exposure to a genotoxic carcinogen. The process from carcinogen exposure and tumor formation may follow predictable sequences of cellular events involving differential gene expression with different sequences occurring with different mechanism of action. Complementary DNA (cDNA) microarray technology, can be used to analyze such changes in genome-wide patterns of gene expression between treated and control groups. Toxicogenomics using microarray technology may be able to identify toxic substances, to identify mechanisms of action, determine no effect levels, determine susceptible tissues and cell types, and extrapolate effects from one species to another (8). In the related field of pharmacogenomics, microarray analysis gene expression profiles can be used as a proof of principle assay to show an effect of a candidate drug in vivo.

The National Center for Toxicogenomics was established by NIEHS, Research Triangle Park, NC to provide a center of excellence for cDNA microarray technology in predictive toxicology [<http://dir.niehs.nih.gov/microarray/home.htm>]. This project is a natural complement to the long-term program in chemical carcinogenicity and genotoxicity supported by NIEHS and the NTP. One outcome of this project to date has been the development of 'The Toxchip' [<http://ehpnet1.niehs.nih.gov/docs/1999/107-5/innovations.html>]. Early versions of this chip contain over 2000 human genes selected for relevance to basic cellular processes and response to different types of toxic injury including DNA replication, DNA repair, apoptosis, cell cycle control, oncogenes and tumor suppressor genes. New versions of the chip will contain over 12 000 genes. While not intended

to replace short-term genotoxicity or long-term carcinogenicity assays, toxicogenomics could prescreen new chemicals and also reduce the time, expense, and use of animals in the process of drug and chemical development. Many others are involved in the development of cDNA microchip arrays for genomics including academic, governmental, nonprofit and corporate groups. Examples of toxicogenomic research within academic groups include the Department of Biochemistry at Stanford University [<http://cmgm.stanford.edu/pbrown/>] and the Department of Molecular Genetics, Max-Planck-Institute, Berlin, Germany [<http://www.molgen.mpg.de/research/lehrach/groups.html>]. The Microarray Gene Expression Database group provides a forum and structure for exchange of information for workers in the field [<http://www.mged.org>].

Underlying much of the revolution in toxicogenomics and pharmacogenomics is basic work being done in the field of genomic research by such institutions as The Institute for Genomic Research, Rockville, MD [<http://www.tigr.org/tdb>], Celera Genomics, Rockville, MD [<http://www.celera.com>], and by the NCBI, Rockville, MD (www.ncbi.nlm.nih.gov). NCBI has developed programs such as the Gene Expression Omnibus to support the public use and dissemination of gene expression data, to build a gene expression data repository, and to provide an online resource for the retrieval of gene expression data from any organism or artificial source [<http://www.ncbi.nlm.nih.gov/geo/>]. Trade associations have established committees to help in the validation of microarray analysis in toxicogenomics. For example, the Health and Environmental Sciences Institute of the International Life Sciences Institute has established a subcommittee called Application of Genomics and Proteomics in Mechanism-Based Risk Assessment Subcommittee [<http://hesi.ilsilife.org/activities/index.cfm>].

Discussion

Clearly many other fine examples of digital and web-based toxicology curricula, tutorials, and

informational resources exist. The number of such resources expands daily, and the compilation provided herein is by no means exhaustive, and due to the transitory nature of many websites, subject to unrestricted changes without notice. These newly available and rapidly evolving digital toxicology resources will no doubt continue to expand the accessibility and usefulness of important human and environmental health related information to a significant segment of the population. It is the belief of the author that this will foster a greater awareness and understanding of important public health issues on the part of students, teachers, health professionals and average citizens alike.

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