REVIEW ARTICLE

New educational strategy in toxicology: the requirements of governmental health care and industrial sectors

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ABSTRACT

Toxicology, as a multidisciplinary field, provides career opportunities for graduates with medical, or veterinarian, pharmacological, pharmaceutical, biological, microbiological, molecular biological, chemical, biochemical, and genetic backgrounds. Today, however, specialists with a university degree in toxicology or a postgraduate training in toxicology have a clear advantage. Postgraduate diplomas are now available in most industrial and even developing countries including Iran. In addition, to be successful, modern toxicologists in the industrial sector also need a good understanding of how to turn a scientific project into a successful product, an expertise generally acquired by on-the-job training. The rapid progress in essentially all toxicology-relevant sciences makes continuous training mandatory. On the other hand, the governmental health care sector provides rewarding career opportunities for professional toxicologists. Toxicologists in this sector evaluate diverse data on chemicals, assess the risks for exposed populations and assist in the articulation of policies for management of those risks. The latter aspects require extensive experience in health care and environmental fields, awareness of international policies and developments, and ability to communicate risk to politicians and to the public. Education of toxicologists for the governmental health care sector must reflect the broad general and specialist knowledge required.

Key Words *EDUCATION, TRAINING, GOVERNMENTAL TOXICOLOGY, INDUSTRIAL TOXICOLOGY*

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Introduction

Toxicology, the study of poisons, was part of many ancient cultures but was purely descriptive up to the last century (1). Milestones in the development of modern toxicology for the design of industrial chemical products was the proposal of the task force after the fatalities with a sulfanilamide elixir in 1937 (2) and some 40 years ago the tragic event of the thalidomide teratogenecity which resulted in a large number of babies with phocomelia (3,4). These catastrophes led to the development of regulation and to widespread discussions on the need of preventive experimental toxicology. As the year 2003 approaches and we think about the challenges the century ahead may hold for toxicology, consideration of the technological advances that have occurred in the last 100 years is a good starting point. These advances have been underpinned by a significant increase in the use of chemicals, and an estimated 90000 chemicals are now in commercial use. Despite the benefits to mankind afforded by these chemicals, concerns surrounding their potential effects on human health and environment have emerged as major policy issues in the early 21st century. Toxicology has developed as a recognizable scientific discipline as a consequence of these concerns. The increasing need for scientific expertise in testing, evaluation and control of hazardous chemicals has resulted in the widespread development of training programs in

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toxicology. Toxicology has come a long way since these 'early' though not so distant, days and has evolved into a scientific specialty of its own (5). Today's toxicologists draw on many scientific approaches from diverse fields such as epidemiology, human and veterinary medicine, molecular biology, genetics, microbiology, chemistry and biochemistry. In addition each of these fields has many sub-specialties and the question is not new (6,7) whether toxicology exists as a separate scientific entity or whether the so-called toxicologists are not just scientists whose only common denominator is their interest in toxicological questions (Table 1). This paper explores the needs of the governmental and industrial sectors for trained toxicologists and the training appropriate to these sectors.

Toxicology in the industrial sector

Today's preoccupation with toxicology is not so much related to natural toxins produced by micro-organisms, fungi, plants or animals, as to those produced by humans. Toxicology has become an important part of the industrial sector, where most of the research on and development of, new chemical, biological and physical agents takes place. These activities aim at promoting progress of mankind, and toxicologists in the industry are expected to recognize potentially harmful effects of these agents early, and to propose measures to control them. To this end, toxicologists in the industrial sector closely collaborate with toxicologists in academic and in governmental agencies. Safety is the primary goal of toxicology, but innovation must always be kept in mind. The development of botulinum toxin into a specialized

TABLE 1 MAJOR EVENTS OF TOXICOLOGY IN PHARMACEUTICAL INDUSTRY

Time	Event	Consequences and status of testing	Professionals
1937	Diethylene glycol poisoning	First toxicologists in the private sector, Mainly acute, subacute and later, subchronic testing	Mainly MDs
Early 1960s	Thalidomide phocomelia	Reproductive toxicity testing, formation of toxicological societies	MDs, DVMs, pharmacists, biochemists, geneticians, statisticians
Late 1970s	Controversy over saccharine carcinogenicty	Importance of mutagenicity and carcinogenicity testing more widely acknowledged	
1980s	Biotechnology	Deviation from standard regulatory testing became necessary, case-by-case approach	
Since mid 1980	Increasing health care costs and competition on the market	Improving of processes to decrease development time and costs: cross-functional development teams with toxicologists	
		Establishment of immunotoxicity testing, worldwide harmonization of guidelines starts	
Since early 1990	Combinatorial chemistry	Several hundred thousands of compounds to be screened in big companies	Increasingly molecular biologists involved
		Functional toxicity testing more widely performed, increasing use of transgenic animals	
	Increasing cost pressure and competition	Mergers and acquisitions; acceleration of process improvement (faster to the market with most profitable compound): establishment of research support including toxicologists	
		Increasing trend for outsourcing of toxicological studies in some companies	

drug for chemical paralysis of uncontrollable spasm is an example, where the elucidation of the mechanism of action of a toxin and the knowledge of toxicokinetics allowed an innovative use (8).

Development of modern toxicology in chemical and pharmaceutical companies

In the 'golden' years of the chemical and in particular of the pharmaceutical industry (1950s-1960s) money was plentiful and regulations were few. Since then, the complexity of development of new projects into marketable products and the requirements for safety have considerably increased the costs, while growing competition on the market, and for drugs the soaring costs of health care exert constant pressure and have decreased profitability. Until a few years ago, a good chemistry laboratory produced up to 100 derivatives of one or several lead structures, which were tested by the pharmacologists on a few rodents for pharmacological action and overt toxicity in acute tests. Early selection of compounds for development often occurred without the involvement of toxicologists. Toxicologists stepped in after selection and put compounds through an increasingly standardized series of toxicological tests ranging from acute to subacute and chronic general toxicity testing, together with genetic toxicity and reproductive toxicity tests. With the arrival of biopharmaceuticals it became evident that standard testing in the sense of a checklist approach was no longer sufficient and those toxicologists must again be more scientific in their approach to prove safety.

With increasing cost pressure, companies also began to wonder how they could avoid the costly failure of projects at late stages of their development. Only 20% of these failures were due to preclinical or clinical toxicity (9), other reasons were being inefficacious in man or failure in marketing, etc. Nevertheless, it was felt that toxicologists should also contribute to the early selection of potential compounds for developments based on early toxicological data. Toxicological screening, though the word was known since the early days of modern toxicology, was increasingly put into practice. In vitro systems were subsequently established and validated in an attempt to save animals and to contain costs.

The scene has changed again considerably with the advent of combinatorial chemistry. Instead of a few hundred early research compounds, several ten or even several hundred thousand early research compounds became available. Obviously that classical toxicology including classical in vitro toxicology using, e.g. conventional tissue cultures are not suited for this type of early compound selection.

With growing complexity of the R&D process and increasing difficulty of turning out novel and commercially attractive drugs, companies realized that intrinsic growth became more difficult. This explains, in brief, the wave of mergers and acquisitions in the chemical and pharmaceutical industry. To manage the resulting large companies in a somewhat difficult environment, new strategies had to be developed. Not surprisingly, today's companies are very much (or too much) involved into improving their processes with the ultimate goal to shorten development time and to concentrate their resources on compounds with a high probability of market introduction and market success, and in this context toxicology must be an efficient and effective partner.

There were other major changes in toxicology, which can not be addressed here such as the introduction of immunotoxicity testing, the refinement of functional testing including safety pharmacology testing, the growing use of transgenic animals, such as 'short term' carcinogenicity assays and international harmonization of testing guidelines.

Toxicology in governmental health care sector

The governmental health care sector toxicologist or regulatory toxicologist supports the government in reaching sound regulatory decisions on the risks to human health and the environment presented by hazardous chemicals. Career opportunities exist in government services concerned, for example, with control of human and veterinary medicines, assessment of pesticides and biocides, worker or consumer protection, environmental and public health. An apt descriptor of the governmental health care sector toxicologist is 'evaluative toxicologist' (10) or 'administrative toxicologist'. One's evaluates diverse data from all branches of toxicology, makes decisions on their quality and acceptability, draws appropriate conclusions and provides advice that may have far-reaching consequences. The regulatory toxicologist's primary function is to assess data generated by other toxicologists in industry or academic institutions. The opportunities for independent research into toxicological problems are limited, other than in conjunction with

TABLE 2 TASKS OF THE GOVERNMENTAL SECTOR TOXICOLOGIST*

Tasks
Identifiacation of the (eco) toxicological hazards of chemicals
Risk assessment
Recommendations for risk management
Assessment of chemical safety data sheets (including SPCs for medicinal products)
Classification and labeling of dangerous chemicals
Participation in expert groups
Provision of advice to government, workers, industry, the general public

*Non exhaustive list

TABLE 3 CORE TOXICOLOGICAL STUDIES REQUIRED FOR REGISTRATION OR NOTIFICATION OF A NEW INDUSTRIAL CHEMICAL, MEDICINAL PRODUCTS OR PESTICIDE*

Endpoint	Industrial chemical	Medicinal product	Pesticide
Acute toxicity	R	R	R
Repeat dose toxicity	R		R
Toxicokinetics	Preliminary assessment	R	R
Irritancy/corrosivity	R	Dependent on use profile	R
Sensitising properties	R	Dependent on use profile	R
Phototoxicity/photoallergenicity	×	Dependent on use profile	R
Genotoxicity	R	R	R
Carcinogenicity	Tonnage-and exposure-triggered	R	R
Reproductive effects	Tonnage-and exposure-triggered	R	R
Special studies/target organ including neurotoxicity	Triggered by results of repeat-dose toxicity/chemical class	Triggered by results of repeat-dose toxicity/chemical class	Triggered by results of repeat-dose toxicity/chemical class
Observations in humans	As available	R	R
Ecotoxicity	R	R	R

*Dependent on field of drug application. R=Required

range from identification of the intrinsic hazards of a chemical to assessment of its risks for potentially exposed populations and articulation of policies for management of those risks. Table 3 illustrates the diversity of typical data assessed toxicology, such as genotoxicity, carcinogenicity, re academia or industry. Tasks, as listed in Table 2, by regulatory toxicologists in the areas of control of new industrial chemicals, medicinal products and pesticides. Specialization in specific areas of toxicology, such as genotoxicity, carcinogenicity, reproductive toxicology, is desirable and may be feasible in large regulatory agencies. However re- gulatory agencies, whatever the area of control, tend to employ relatively limited numbers of toxicologists. Toxicologists in smaller regulatory agencies must have the competence to assess all of the toxicological studies carried out on a particular chemical. A broad knowledge base is required to evaluate such data.

The identification of the intrinsic hazards of a chemical based on the assessment of available toxicological data on that chemical requires a broad training in toxicology as outlined in 'training programs for regulatory toxicologists' below. The competencies necessary for the risk assessment and risk management phases of chemical control require extensive experience in the regulatory field, awareness of national/ international policies and developments, and ability to communicate risk to politicians and the

TABLE 4 PROFESSIONAL REQUIREMENTS FOR TOXICOLOGISTS IN INDUSTRIAL SECTOR (OVERVIEW)

Training	Variant*	Requirements
Basic university training	(A)	Veterinary or human medicine, biology, microbiology, molecular biology, physiology, pharmacology, pharmacy, chemistry, biochemistry, etc.
	(B)	Specialized education in toxicology-relevant sciences
Post-graduate training	(A)	Postgraduate training according to Table 3; Ph.D. useful
	(B)	Further training optional; Ph.D. useful
Training on the job	(A) or (B)	Study director, expert writer, toxicology representative on cross-functional research/development teams Certification as toxicologist after ~ 5 years
Continuous education on the job	(A) or (B)	Proof of continuous education and activities: such as attendance of scientific events, involvement in toxicological studies and evaluation, writing of publications and internal reports Re-certification as toxicologist after ~ 5 years (regulations depend on the certifying body)

*Variant (A) and (B) always refers to the basic university training: (A) in biological sciences other than toxicology or chemistry; (B) specialized in toxicology.

general public. This experience is gained by a combination of 'on the job' training, participation in specialist training courses and interchange of views with other senior regulatory toxicologists.

Governmental sector toxicology has placed increasing emphasis on risk assessment in recent years. Risk assessment is inherent to the process of achievement of sound regulatory decisions on the risks to human health and the environment presented by hazardous chemicals. It involves identification of the intrinsic hazards of the chemical, identification of the intrinsic hazards of the chemical, the likely exposure and the margin of safety between the anticipated level of exposure of the population at risk and the level of no-observed-effect established in toxicological studies. The approach to risk assessment and the decision-making logic may be slightly different within the different areas of regulatory toxicology, such as medicines control, industrial chemicals and pesticides or biocides. For example, a decision may be taken to authorize a medicinal product, which has been shown to have carcinogenic effects in animal studies, dependent on a risk-benefit analysis, knowledge of the mechanism of carcinogenicity in the animal and the therapeutic ratio. A pesticide having a similar toxicological profile that may potentially be present in products to which the general public is exposed is unlikely to achieve regulatory acceptance on the basis of an assessment of the risks. Training in risk assessment is particularly important for the governmental health care toxicologist.

Teaching requirements for toxicologists working in the industrial sector

There is a continuing need for toxicologist in the industrial sector in chemical or pharmaceutical companies.

A solid background in the biological sciences remains a key element. It is not sufficient to establish complex testing systems and to simply generate data, but the data must be interpreted as to their relevance to the biological systems exposed. Professional requirements for toxicologists working in the industry are therefore high: besides basic university education in a field relevant to toxicology, postgraduate training and experience on the job are essential (Table 4) (11). A Ph.D. degree in toxicology or a related field is of advantage, because the candidate has acquired

TABLE 5 TYPICAL CAREER LIFE CYCLE OF TOXICOLOGISTS IN INDUSTRIAL SECTOR

Time	Typical activity
During the first years	Study director in investigative toxicology (trouble solving) or regulatory toxicology (formally required investigations)
After 3-5 years on the job	In addition to the line function (see above) toxicology or drug safety representative on cross-functional project teams interfacing research and development or on development project teams
Mid-professional life	Full time drug safety representative on cross-functional teams for key development projects or for supporting therapeutic areas in research; involvement in major trouble-solving activities
Mature professional life	As above; senior drug safety expert; author particularly of difficult expert reports and company representative for difficult negotiations with governmental authorities; representative on important working groups establishing, such as new regulatory guidance May become self-employed and work as an independent drug safety consultant May change professional direction and assume. Such as higher management responsibilities

experience in doing independent research, in assessing the data and in summarizing the conclusions in written form.

The traditional areas of toxicology related to general and reproductive toxicity as well as mutagenicity testing remains very important. However, because of the nature of the compounds that are selected for their high biological efficacy, many compounds also have significant biological side effects, which need to be investigated with regard to their pathogenesis and relevance to the biological target system. Therefore, besides regulatory toxicology, experimental toxicology is well established for many years in larger chemical and pharmaceutical companies and has attracted scientists from many different scientific disciplines across the whole scientific life science spectrum and chemistry. In addition, a number of years ago, some pharmaceutical and chemical companies have begun to set up groups working in molecular toxicology with tools for gene analysis, gene expression and proteomics, to investigate early toxic events at the molecular level (12). Thus, besides medical and biological professions, post-graduates (such as with a biochemical, genetic or molecular biological background) are in high demand.

Toxicity screening for early selection of compounds for development, regulatory testing and trouble solving all require toxicologists capable of setting up the necessary test systems, knowing their endpoints and limitations, and analyzing and interpreting results obtained by various methods in vitro and in vivo. Extrapolation of experimental data to man and risk assessment capabilities are of particular importance; specialists with a university degree in toxicology or a postgraduate training in toxicology are much needed (11,13-16).

Certification of toxicologists, though an old postgraduate (17,18), has become a buzzword for several reasons. The name 'toxicologist' cannot yet be protected, but a 'certified by' followed by a well recognized institution (such as professional society or university) provides some reassurance as to the training qualifications of the person concerned (20-25). It is also foreseeable that regulatory agencies will pay more attention to the credentials of toxicological experts who submit registration documents.

These days most pharmaceutical and chemical industries in the west have matrix-type organizations, in which specialists often are members of research or development teams in addition to their classical function tasks. The objective of these teams is twofold: (a) to facilitate selection of early compounds based not only on their pharmacological action, but also taking into account their toxicity potential, ADME parameters, their physicochemical properties affecting synthesis and formulation, registrability and marketability, among others;

and (b) to develop selected compounds into registrable and marketable products. To be successful, these people need a broad scientific and business related understanding and must be familiar with regulatory requirements and modern schemes for developing chemicals and drugs. Effective working in, and management of, teams as well as negotiation and communication skills are essential. Such capabilities are generally acquired by on-the-job training, including job rotations, such as drug regulatory affairs, pharmacology or technical development departments. Major progress was achieved in essentially all toxicology-relevant sciences, particularly during the past decade. This necessitates continuous training of all scientists and even of administrators involved in toxicity testing an old topic as well (19). Many toxicologists in the industrial sector go through some kind of career life cycle (Table 5), which differs somewhat from a toxicology career in the governmental sector (26). Typically they start off as study director for regulatory or exploratory (trouble-solving) studies. With increasing experience on the job, they might then take over, in addition to their task, responsibilities as toxicology or drug safety (e.g. drug metabolism) representatives in cross-functional teams established in the matrix systems of modern companies. The early selection and early development process both require a broad scientific knowledge as well as good intuition to what is achievable (27). For later phases of development good organization skills paired with trouble solving and negotiation capabilities are essential. Almost all pharmacologically highly active compounds will show some kind of toxicological hurdle. If not properly addressed by additional investigative studies to elucidate the pathogenesis and to obtain further insight into the relevance of the finding for higher biological systems such as man in the case of pharmaceuticals, such hurdles might be prohibitive.

Initially, project team responsibilities might be limited to smaller projects. With increasing experience the toxicologist then might move as a full time occupation into key project teams or into teams managing the difficult transition from a research to a development compound as described above The proof that somebody has really become an expert toxicologist is the moment when he or she is entrusted with writing expert opinions or an expert report addressed to the regulatory bodies around the world for registration of new products. An expert reports is a final critical scientific assessment of toxicology and drug metabolism data gathered over many years at a cost of millions of dollars. The data must also be evaluated in the context of the pharmacological action of the compound in question, its intended therapeutic use, the available clinical data, etc. The limitation of the assessment to some 25 pages renders the task even more demanding. The expert is then often called upon to present the case in hearings with regulatory bodies or to prepare answers to questions on these bodies. The number of questions not anticipated is often inversely correlated with the experience of the expert.

In addition, chemical and pharmaceutical companies often require great flexibility of their associates and ask them to take over new responcurrent company needs. At later stages of their career some toxicologists move into the drug regulatory field, act as quality assurance manager; take over personnel responsibilities in areas outside of toxicology, to satisfy current company needs. At later stages of their career some toxicologists move into the drug regulatory field, act as quality assurance manager, take over personnel responsibilities or large portions of the company, move into purely management positions such as site management act as process improvement managers, become members of the company boards, etc. With a rapidly changing environment the number of scientists including toxicologists who will move into new areas of professional activities even more than once, will increase.

Teaching requirements for toxicologists working in the governmental health care sector

Education of toxicologists for the governmental health care sector must reflect the broad general knowledge required. Key elements for the toxicologist include chemistry, biology, biochemistry, physiology, anatomy, laboratory animal science, genetics, molecular biology, microbiology, histopathology, hematology, pharmacology, genetic toxicology, reproductive toxicology, carcinogenicity, immunology, general toxicology, law and regulations (28). The ecotoxicologist may come from an environmental science background, involving training in many of the elements listed above but also specific training in ecotoxicology/environmental toxicology.

The most common route for toxicologists to enter toxicology is via graduation in the basic

TABLE 6 SOME CHALLENGES FOR TOXICOLOGISTS IN THE INDUSTRIAL SECTOR OVER THE COMING YEARS

Trends	Required skills/actions
Combinatorial chemistry becomes more important	Develop and refine relevant, reliable and fast screening systems which need minimal amounts of a compound for detecting possible toxicological effects
Computational modeling of adverse effects	Refine and extend computer models mimicking and predicting potential toxic effects in biological systems; extend the necessary databases
Communication of toxicity issues to larger audiences	Ability to simplify complex toxicological issues and interest to communicate the issues and conclusions to a larger lay audience
Further rapid development of toxicology-relevant sciences	Life-long interest in learning; vision to anticipate applications of new scientific insights obtained in other fields for toxicology; willingness to maintain a high professional and ethical standard and certification

sciences, medicine or veterinary medicine, with specific postgraduate experience in toxicology. The latter may involve a postgraduate quailfication by research in the field of toxicology, or a postgraduate qualification obtained by participation in a taught postgraduate program. Such programs are now available at a number of academic institutions throughout the world. Specific undergraduate programs in toxicology are now becoming more common, and toxicology is also being included as a component of degree programs such as pharmacology, biochemistry, medicine, and veterinary medicine. It is generally accepted, however, that postgraduate experience is an essential prerequisite for the individual seeking a career in regulatory toxicology, and many regulatory toxicologists will also have ex perience of working in industry or in contract sibilities in areas outside of toxicology, to satisfy toxicology.

Specialist expertise in a particular discipline of toxicology such as genetic toxicology or toxicological pathology may have been acquired by, for example, postgraduate research in a particular discipline. It is highly desirable to have specialist expertise covering the major areas of toxicology represented within a regulatory team. As indicated previously, this may not always be achievable, particularly in small countries. For this reason some governmental/health care sector toxicologists may elect to use the services of academic toxicologists for particular problems. However, they must be sufficiently aware of developing issues in toxicology to know that specialist input into a problem should be sought. Short-term training courses in advanced toxicology are invaluable in developing such awareness, as is participation in international conferences such as EUROTOX.

In relation to the critical phases of risk assessment and risk management, the necessary experience is gained by a combination of 'on the job' training, participation in specialist training courses and interchange of views with other senior regulatory toxicologists. Training in risk assessment is particularly important for the regulatory toxicologist, as already indicated above. The risk assessment summer schools (RASS) organized by IUTOX make a significant contribution in this regard, particularly for regulatory toxicology from developing nations.

Discussion

The governmental health care sector is a source of rewarding and varied career opportunities for the professional toxicologist. Governmental secsector toxicology requires a broad knowledge of the subjects together with specialist knowledge relevant to the particular regulatory area. The necessary experience is obtained by undertaking training programs in toxicology at undergraduate and postgraduate level and (optionally) postgraduate research. Short-term training courses in

advanced toxicology, risk assessment and other relevant topics, together with 'on the job' training are essential for the development of the expertise necessary to become a senior governmental sector toxicologist interested in the risk assessment and risk management of hazardous chemicals. In addition the future of toxicologists in industrial sector is promising. The current trends in the pharmaceutical and chemical industry require further adaptations (Table 6). In particular there is a need for better screening systems, as already available for pharmacological screening (29,30). Such systems must allow the screening of larger numbers of chemicals in minimal amounts rapidly, economically and reliably. Significant progress can be expected in the coming years based on our increasing understanding of the molecular basis of toxicology. Scientists with an excellent understanding of molecular physiology and pharmacology and an interest in toxicological issues are very much in demand.

Computational modeling will reach a more mature stage over the coming years (31). Structure-activity relationship (SAR) databases are now already well established and will continue to grow, thus making the SAR approaches more reliable. Modeling of pharmaco- and toxicodynamic events in biological systems has evolved much over the past years and will play an increasingly important role in the future (32). Computational and mathematical skills are highly useful in these areas. Communication of toxicological issues to the public is still unsatisfactory and must be done more professionally (33). The public has become more alert to the increasing exposure to potentially harmful agents and wants to understand the real risk. Misinformation by mass media is still prevailing. People with good communication skills, an excellent understanding of toxicological issues and principles as well as having the ability to correctly simplify complex connections are badly needed.

There is no reason to believe that the rapid scientific development will slow down. Modern toxicologists have to keep up and in the future will have to demonstrate increasingly that they qualify as experts in their field. Continuous education has never been as important as now and will keep this importance. Certification of toxicologist is valid for limited periods only and re-certification needs at least a demonstration of continuous learning, but might also involve passing tests.

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