THREE OPERATIONAL LEVELS IN TOXICOLOGY - AN OVERVIEW

G. VETTORAZZI
World Health Organization
Geneva - Switzerland

INTRODUCTION

The word toxicology occurs ubiquitously in current specialized and layman literature. During the last few years this word has been taken from old treatises on poisons, re-discovered (Aldridge, 1973), re-defined (Anon., 1974), sometimes declared to be essentially indefinable (Anon., 1977), sometimes attempted to be clarified (Murphy, 1978).

In 1974 Norseth (1974) was concerned with the problem of identifying the terms toxicology and toxicologists; if one takes cognizance of the current designations of fundamental aspects and trends in toxicology it can be construed that, apparently, these problems still exist. Thus, in addition to some broad terminology such as forensic, economic and environmental toxicology, one is often asked to draw lines of demarcation on terms such as analytical toxicology, behavioural toxicology, barefoot toxicology (Abbou. 1979), cardiovascular toxicology (WHO, 1979), chemical toxicology (Galli et al., 1978), consulting toxicology, clinical toxicology, developmental toxicology, ecotoxicology (Truhaut, 1977), epidemiological toxicology, extrapolation toxicology, genetic toxicology (Anon., 1978) industrial ecotoxicology (Abbou, 1979), inhalation toxicology, medical toxicology, neurotoxicology (Anon. 1979), nutritional toxicology, occupational toxicology, ophthalmic toxicology (Ballantyne et al., 1977) pharmacotoxicology, predictive toxicology (WHO/FAO, 1974), regulatory toxicology (Vettorazzi, 1978), relay toxicity (Ferrando et al., 1978), statistical toxicology, toxicovigilance (Roche, 1979), tropical toxicology (anon., 1976), et similia. This list should by no means be interpreted as being exhaustive: it is a generally recognized
fact that modern toxicology is a multi-disciplinary field and that it is continuing to expand (WHO, 1979). It must, however, also be recognized that the initiated as well as the non-initiated may find it difficult to understand what it is all about.

THE CONCEPT OF TOXICOLOGY

When sentences containing the words "toxicology" and "toxicologist" are utilized in the technical literature, it is generally easy to identify the specific area to which the individual terms are related. Thus, if a scientific article reports findings in experimental studies on laboratory animals aimed at assessing the acute toxic effects of a substance by the inhalation route, it implies that what it is dealt with relates to the field of experimental toxicology/inhalation toxicology/acute toxicity.

When the terms "toxicology" and "toxicologist" are used in administrative papers some confusion can arise deciding if the term should be taken as all encompassing or restricted. If one goes from the title to the body of the paper and reads carefully, in most cases, all uncertainties will be resolved. Three important reports may serve as examples for this need of interpretation, namely, a report on collaborative research in toxicology from a meeting of the European Medical Research Council (anon., 1974), a report on medical surveillance of population exposed to toxic risks (Roche, 1979) and a report on manpower developments in toxicology (WHO, 1979). In the first the word "toxicology" in the title of the report appears to be related mainly to experimental toxicology; in the body of the report it becomes clear that the word also implies to several other areas such as clinical, medical, occupational and environmental toxicology. In the second, while the title seems to imply mainly medical aspects of toxicology under a new expression "toxicovigilance", from the body of the report it appears that all areas of toxicological expertise are equally included. Finally, in the third report, while the term "toxicology" in the title appears to be all encompassing, in the text the term is restricted mainly to environmental and regulatory toxicology,
with some reference to occupational toxicology but with explicit exclusion of forensic and clinical toxicology.

It is, however, when decisions are taken regarding the assessment of individual expertise that problems of identify may cause serious confusion. For instance, a medical toxicologist from a hospital emergency room and an experimental toxicologist from an animal testing laboratory both fall into the category of "toxicologists", however, the areas of expertise are quite different and operational assignments implying exchange of roles without adequate training might cause critical difficulties. Similarly, it does not appear advisable to request occupational toxicologists to conduct tests and to assess the significance of findings obtained in genetic toxicology without previous adequate training. It follows that the term "toxicologist" without specifying the areas of expertise does not convey enough information for operational purposes. It should be recognized that toxicology has previously lacked from identification as a specific entity, and few training institutions have established separate units or departments of toxicology. Most have included toxicology in existing organizational structures and titles. While this situation has added strenght to the interdisciplinary nature of toxicology, it has at the same time severely restricted its efficient growth (Oehme, 1979) and it might at times have generated confusion.

As a contribution to clarification, the author propose that for operational purposes "toxicology" can be separated into three different levels making use of three variables, namely, dose, time of exposure and magnitude of the population involved. The sequential numbers, first, second and third are not meant to indicate any order of importance.

**THE THREE LEVELS OF TOXICOLOGY**

**First Level**

The first level is mainly characterized by very high doses, very short time of exposure and relatively small sector
of population involved. It is the case of acute poisoning, accidental or voluntary in which symptomatic or specific therapies are applied including all those emergency measures available which are aimed at bringing back, whenever possible, the vital functions of the patient. When the victim is still alive, the management of poisoning is generally left to the care of the medical toxicologist; in case of death from unknown or suspected poison due to successful suicide, homicidal poisoning or other situations involving legal responsibilities the intervention of the forensic and analytical toxicologist might be necessary. This first level of toxicology is mostly the domain of the experienced physician adequately trained in medical and forensic toxicology. On a worldwide scale, expertise in this field is being promoted by the World Federation of Associations of Clinical Toxicology Centers and Poison Control Centers and similar associations.

It is realized that it would be an over-generalization to characterize this level solely by dose, time of exposure and sector of population involved since it also highlights the physician-patient relationships; thus, for the sake of completeness this level may include aspects such as biochemical and clinical diagnoses of intoxications, rehabilitation techniques, specific antidotes, and management of sequelae arising from any dose (high, moderate, small) or time of exposure (acute, sub-chronic, chronic) if the insurGENCY of signs and symptoms should require clinical care.

Second level

The second level is characterized by smaller doses than those which may cause acute toxic phenomena, longer time of exposure and wider sector of population involved. It is the case of occupational exposure (occupational, industrial toxicology) in which a person is exposed to a known substance at identifiable and, in principle, controllable concentrations or the case of clinical toxicology as applied to clinical assessment of drug efficacy/toxicity under controlled conditions.
The occupational and clinical toxicologist is mainly concerned with routine examinations of exposed individuals with the expectation that examination of the normal health parameters will reveal anomalies which could be attributed to causative agents the biological effects of which in man are completely unknown, only partially known or suspected. It has been recommended that qualified personnel working in occupational health should also receive adequate training in the basic principles of toxicology including the concept of dose-response (uptake/effect and uptake/response, etc.) relationships, the major adverse reactions that could occur in man, species variations in effects, pharmacokinetics, and primary elements of epidemiology (WHO, 1979). Obviously, this second level represents the most fertile ground for the development of sound epidemiological information. Similarly, special training is recommended for the personnel undertaking clinical evaluation of drugs for use in man (WHO, 1970; 1975). In addition, toxicologists operating at this level are faced with ethical and legal aspects (justification) and purposes for clinical trials of drugs; setting health-based permissible levels for occupational exposure; etc.) as well as with pre-clinical toxicological trials (animal experimentation); it is thus in the interest of these toxicologists to keep in close touch with regulatory and experimental aspects of toxicology.

**Third Level**

The third level is characterized by very low doses, extremely long period of exposure (often the whole lifetime) and very wide sector of population. It is the case of environmental toxicology as applied to the assessment of long-term effects in man resulting from a long period of exposure to very low doses of agents found in food, water and air. Examples are the carcinogenic, mutagenic and teratogenic effects which are insidious, hard to predict and for which the levels of exposure to the causative agent are very low but the period of exposure may be of very long duration. To complicate things further, effects observed after short-term exposure may be encountered after exposure at lower levels but for longer periods of time.
As a generalization, while the first level of toxicology stresses the clinical and hence curative aspects and the second level places emphasis on preventive aspects through close epidemiological observations, the third level attempts to establish preventive criteria mostly utilizing experimental models to assess the long-term impact on man of continuous exposure to agents such as industrial products (pesticide residues, food additives, cosmetics, household chemicals, drugs, etc) and environmental contaminants originating from both natural and industrial sources. This third level is rather new and it represents a challenge to modern experimental and regulatory toxicologists who attempt to find answers to the increased concern about toxicity and chronic disease as potential consequences of exposure to chemicals.

The historical development of this third level coincides with: (a) the intensive use of chemicals in industrial manufacturing and agriculture, with attendant problems related to biopersistent compounds occurring as environmental pollutants which, in turn, may enter the food chain; (b) the establishment of regulatory activities in food and drugs by many industrialized countries; and (c) the awareness that our entire world is composed of chemical and that much of it is contaminated with low levels of persistent compounds that for the most part did not exist as contaminants fifty years ago. A substantial contribution to the development of modern experimental toxicology and risk assessment came from the establishment of "toxicological testing protocols" by national regulatory agencies as well as from enactments of several laws (Table I). On the international scale, important contributions were received from the activities of the joint FAO/WHO Expert Committee on Food Additives (1959-1980) which introduced the concept of "acceptable daily intake" (ADI) as a long-term safety index for chemicals in the diet, the Joint FAO/WHO Meeting on Pesticide Residues (1963-1980) which applied the concept of ADI to pesticide residues and developed international "maximum residue limits" (MRL) for the most commonly used agricultural pesticides, and several important activities of WHO Scientific Groups on drug toxicity (WHO, 1966, 1967; 1968; 1969; 1971; 1975).
The toxicologists operating at this level belong to a variety of specialized branches of toxicology, have diverse educational background and have practical experience developed over many years. Interpretation of experimental findings, extrapolation processes inter and among animal species, risk assessment for human population, estimation of potential toxicity, the political and economic consequences resulting from toxicological decisions (risk-benefit) and other problems are difficult matters. This may explain why toxicologists operating, at the first and second levels feel often uneasy when called to contribute expert judgements on questions related to the third level. It is particular to toxicologists of the third level that the sentence attributed to the late Dr. Arnold J. Lehman (1900-1979) applies: "You too can become a toxicologist in two easy lessons - each of them lasting 10 years".

REFERENCES


Anonymous - Proceedings of the First Congress on Tropical Toxicology. Manaus, Brazil, April 11-14, 1976


Ferrando, R., Truhaut, R., Raynaud, J-P. and Spanoghe, J-P. - Toxicity by relay. III Safety for the human consumer of the use of Carbadox, a feed additive for swine, as estimated by a seven year relay toxicity on dogs. Toxicology, 11, 167-183, 1978


Murphy, S.D. - What have we accomplished as a professional society? Veter. Hum. Toxicol., 2, 333-336, 1978

Norseth, T. - Personal identify, a problem for the toxicologist? In: EMRC (European Medical Research Council) Subcommittee Report on Collaborative Research in Toxicology. Addendum 8, EMRC 74/19 1974


### TABLE 1

<table>
<thead>
<tr>
<th>Country</th>
<th>Law / Act</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Environmental Contaminants Act</td>
<td>1974</td>
</tr>
<tr>
<td>France</td>
<td>Control of Chemical Products Act</td>
<td>1977</td>
</tr>
<tr>
<td>Federal Republic of Germany</td>
<td>Chemicals Act</td>
<td>Pending</td>
</tr>
<tr>
<td>Japan</td>
<td>Chemical Substances Control Act</td>
<td>1973</td>
</tr>
<tr>
<td>Sweden</td>
<td>Act on Products Hazardous to Man and the Environment</td>
<td>1973</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Law on Trade in Toxic Substances</td>
<td>1969 (effective 1972)</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>Toxic Substances Control Act</td>
<td>1976</td>
</tr>
<tr>
<td>Denmark</td>
<td>Toxic Chemicals Act</td>
<td>Pending</td>
</tr>
</tbody>
</table>