Korean J. Toxicol
Vol.2, No.2, pp. 103-111, 1986

COMPARISON OF THE EEC AND US SYSTEMS FOR SAFETY EVALUATION PROCEDURES AND REGULATIONS INVOLVING DRUGS AND INDUSTRIAL CHEMICALS

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TESTING CONCEPTS

The history of modern toxicology was decisively influenced by a string of tragic accidents. As a consequence, government health authorities have long held the opinion that the toxicological assessment of chemicals could not be left entirely to the scientific community and the interested industry, but was a public concern, and thus had to be subjected to strict regulations.

Official testing requirements were first established for biologically active substances such as drugs and pesticides, and agents to which large populations were exposed, *e.g.* intentional and unintentional food additives.

Later, safety testing became important also for industrial chemicals, environmental pollutants, cosmetics, and flavors, and very recently, concepts are developed for the evaluation of substances produced by recombinant DNA and other biotechnologies.

In order to permit an effective control, it was necessary to have experimental testing procedures that could be recommended to industry and public research institutions. Testing guidelines were, therefore, worked out by different bodies such as regulatory agencies (1), international expert committees, eg. the FAO/WHO Joint Expert Committee on Food Additives (JECFA) (2), and industry–sponsored organizations (3, 4). Despite the fact that the chemical and biological properties of the compounds ranged over a very broad spectrum, that the uses of the substances were vastly different, that the size and the type of the exposed populations varied and that the exposure levels extended over a very broad range, a remarkable uniformity of the basic approaches to toxicity testing has emerged. This is illustrated by a statement taken from the report of the Scientific Committee of the Food Safety Council (4) which reads as follows:

> *"Presented in this report is a system of estimating the risk offered by the ingestion of any component of food. It is applicable whether the substance is a normal ingredient, an additive, an environmental contaminant, a natural toxicant, a pesticide, a packaging constituent which transfers to food, or any other substance which is likely to be in food."*

What this, in fact, says is that the same safety assessment concepts can be used for all chemicals in food ranging from the most toxic compounds known to man, such as the aflatoxins and botulinus toxin, to the essentially non–toxic agents, e.g. starches, sugars and certified food colors. It is clear that such an attitude has little scientific merit, but is expedient and of great convenience to regulatory bodies and the industry. In addition, it facilitates mutual acceptance of research data, and thus, contributes to the expansion of international trade.

The safety assessment procedures currently used are summarized in Table 1. They include tests designed to detect systemic and local toxicity including sensitization potential, disturbances of reproductive processes, mutagenicity and carcinogenicity. As a general rule, toxicological investigations are conducted over a broad range of dosages and concentra-

Table 1. Standard testing procedures used for safety assessment of chemicals.

Systemic toxicity:	single–dose (acute), and repeated–dose (subacute, subchronic, and chronic) studies.
Inhalation toxicity:	single–and repeated–dose studies.
Local toxicity:	dermal and mucosal irritation studies, incl. phototoxicity. dermal sensitization studies incl. photoallergy. subcutaneous, intramuscular, intravenous irritation studies
Reproductive toxicity:	fertility, general reproductive performance, teratogenicity and peripostnatal studies.
Mutagenicity:	in vitro and in vivo assays for various genotoxic end–points.
Carcinogenicity:	life–time rodent carcinogenicity bioassay
Safety pharmacology:	various functional models.

Table 2. Duration of repeated dose toxicity studies for drugs EEC Council recommendation, October 26, 1983 (rodent and non–rodent species).

Proposed duration of human treatment	Suggested duration of repeated dose toxicity studies
1 or several doses within a day	2 weeks
repeated doses for up to 7 days	4 weeks
repeated doses for up to 30 days	3 months
repeated doses beyond 30 days	6 months

tions, including levels that cause measurable functional toxicity to the animals or demonstrable lesions in target tissues. In recent years, stringent rules for good laboratory practices have been developed and are now applied on a worldwide scale.

SAFETY TESTING REQUIREMENTS

Although the basic approach to toxicological testing is identical for all classes of chemicals, the extent of the experimental program varies, depending on the nature of the product, the stage of the development, the size of the exposed population, the exposure levels, and even the size of the yearly production. For example, in many countries, the duration of repeated–dose toxicity studies of new drugs depends on the anticipated duration of human therapeutic administration. Table 2 summarizes the current requirements of the member states of the European Economic Community (EEC)(5). Most of the other Western European countries implicitly adhere to these rules. In the USA, on the other hand, a somewhat more complicated set of requirements exists (6). It takes into account not only the anticipated duration of therapeutic administration, but also the phase of development (Table 3). It is noteworthy that the USA, in practice, requires for many drugs repeated–dose toxicity studies lasting at least 12 months, whereas in Europe, it is generally felt that a six month study provides sufficient information on chronic toxicity of most drugs, with the exception of data on the carcinogenic potential.

An interesting example of how various factors may influence the extent of safety testing is contained in a recent publication of the Bureau of Foods of the US Food and Drug

Table 3. Safety studies required by the US Food and Drug Administration for drugs. (oral and parenteral administration) (rodent and non–rodent species).

Duration of human administration	Phase of clinical investigation	Repeated–dose toxicity studies
several days	I, II, III, NDA	2 weeks
up to 2 weeks	I	2 weeks
	II	up to 4 weeks
	III, NDA	up to 3 months
up to 3 months	I, II	4 weeks
	III	3 months
	NDA	up to 6 months
6 months to unlimited	I, II	3 months
	III	6 month or longer
	NDA	18 month rodent
		12 month non–rodent

Note: this list does not contain required studies on carcinogenicity.
NDA = New Drug Application

Administration (7). It relates the requirements for safety data of food additives and color additives used in food to "concern levels" which are briefly characterized in Table 4. Three categories of additives are identified according to the chemical structure, the contaminants, and the known or predicted metabolites. The "concern levels" are determined individually for the structure categories according to the magnitude of dietary exposure. The extent of toxicity testing deemed to be necessary for compounds assigned to the 3 "concern levels" are shown in Table 5.

No comparable rating system exists in Europe. The requirements for safety testing of food additives, although somewhat standardized by current EEC guidelines, are handled individually by the various states. Recommendations by the JECFA are usually taken into consideration. However, acceptable daily intakes (ADI) determined by the JECFA are not automatically applied by the various national regulatory agencies.

The extent of safety testing required by regulatory agencies is sometimes influenced by the magnitude of the yearly production. This is the case for industrial chemicals manufactured and registered in the Federal Republic of Germany. The basic concepts of this regulation are summarized in Table 6.

NATIONAL DIFFERENCES IN SAFETY TESTING REQUIREMENTS

Although it would be highly desirable that the same safety data would be demanded by all countries, it is an undeniable fact, that we are still far away from a harmonization of testing requirements. The Organization for Economic Co–operation and Development (OECD) has made a valiant effort to develop testing standards and guidelines which would permit mutual acceptance of data (8). However, this international organization cannot influence the way national governments interpret the experimental results generated according to the OECD testing rules. For example, all member states of OECD have accepted toxicity

Table 4. "Concern Levels" determining the extent of toxicity testing of food additives and color additives used in foods. Bureau of Foods, US Food and Drug Administration 1982.

Structure Category		
C	B	A
		Concern level III 1.0 ppm, 0.025 mk
	Concern level III 0.5 ppm, 0.0125 mk	
Concern level III 0.25 ppm, 0.0063 mk		
		Concern level II 0.05 ppm, 0.0012 mk
	Concern level II 0.025 ppm, 0.00063 mk	
Concern level II 0.0125 ppm, 0.00031 mk		
		Concern level I
	Concern level I	
Concern level I		

ppm: parts per million dietary exposure to the additive
mk: mg/mk/day or more
Concern level I: less than limits of concern level II.

Table 5. Safety testing requirements for food additives and color additives in foods. (Bureau of Foods, US Food and Drug Administration, 1982).

Safety Tests	Concern level		
	I	II	III
Short–term feeding study, 1 rodent spec.	×		
Short–term tests for carcinogenicity	×	×	×
Subchronic feeding study, 1 rodent spec.		×	
Subchr. feeding study, 1 non–rodent spec.		×	
Multigeneration reproduction study with teratology, 1 rodent species		×	×
Chronic feeding study, 1 rodent species			×
Chronic feeding study, 1 non–rodent spec.			×
Carcinogenicity studies, 2 rodent species			×

Note: Depending on outcome, additional studies may be required.

Table 6. Testing requirements for industrial chemicals in the Federal Republic of Germany.

Basic requirement:	Acute toxicity (1 species) Short term mutagenicity tests Irritation potential Subacute toxicity (1 species)
100t/year or 500t total	Subchronic toxicity Fertility Teratogenicity Carcinogenicity Ecotoxicity
1000t/year or 5000t total	Chronic toxicity Acute and subacute toxicity, 2 species Behavioral toxicity Toxicokinetics Additional Ecotoxicity

guideline Nr 401, describing the method of oral acute toxicity testing and determination of a median lethal dose (LD50). However, the classification of hazardous chemicals and labeling requirements based on the LD50 values is markedly different in various countries (Table 7).

In Europe, there is an unfortunate competition between various international organizations, concerned with determining toxicity testing requirements. Originally, the World Health Organization (WHO) expert committees had the leading role. Now, other organizations have become active, in particular the OECD and the European Economic Community (EEC), but also other groups of states. As an example, the most recent decision (1986) of an OECD expert committee on acute toxicity testing shall be mentioned. This group accepted unanimously a revision of the testing guideline Nr 401 (Table 8). Nevetheless, the EEC, although it was represented at the OECD meeting, has started to work out its own version of an acute toxicity testing guideline. In addition, the USA representative at the OECD expert committee meeting also agreed with the revision; however, he could not commit himself that the various governmental regulatory agencies in his country could all be convinced to endorse the new rules.

It is often difficult to determine what the reasons for national preferences and single-handed efforts in safety testing requirements are. An important aspect is the allocation of responsibility. In some countries, industry, the scientific community and the health profession are primarily responsible for the safe use of chemicals of all kinds. In other states, the major responsibility is vested in governmental regulatory and control agencies. As an example, the notification and approval procedures for testing new drugs in man are shown in Table 9.

As a final example, safety testing requirements for field testing and registration of new pesticides are summarized in Table 10.

Table 7. Criteria for classification of toxic chemical (LD_{50} oral).

United Nations Recommendation	EEC Norway Sweden	US Consumer Protection Label	Swiss Toxic Substance Label	Japan Toxic and Delet. Subst. Label
Group I 5 mg/kg Group II 5–50 mg/kg Group III 50–500 mg/kg (solids) 500–2000 mg/kg (liquids)	Very toxic 25 mg/kg toxic 25–200 mg/kg harmful 200–2000 mg/kg	highly toxic 50 mg/kg	Category I 5 mg/kg Category II 5–50 mg/kg Category III 50–500 mg/kg Category IV 500–2000 mg/kg (products) 500–5000 mg/kg (substances) Category V 2000 mg/kg (products) 5000–15000 mg/kg (substances)	Toxic Subst. 30 mg/kg Deleterious 30–300 mg/kg

(OECD, internal report 1983)

Table 8. OECD Testing Guideline 401, "Acute Oral Toxiciy". (Proposed Revision 1986).

Animal species:	rodents
Number:	at least 5 per dose
Dose levels:	at least 3
Sex:	1 sex, cross check for marked sex difference at 1 dose level
Limit test:	1 dose level of 2000 mg/kg, both sexes
Special remarks:	highly irritant and corrosive substances must only be tested at doses with acceptable local tolerance. Animals showing severe and protracted signs of distress must be killed.

Table 9. Notification and approval procedures for testing of new drugs in man.

Country	Notification	Regulatory Review	Approval	Remarks
Austria	+	–	+	1
Belgium	+	–	+	2
FRG	+	–	–	3
France	+	–	+	4
Italy	+	–	+	5
Portugal	–	–	–	6
Spain	+	+	+	
Sweden	+	+	+	7
Switzerland	–	–	–	
The Netherlands	–	–	–	8
United Kingdom	+	+	+	9
USA	+	+	+	

1. Application goes to Drug Advisory Committee
2. Review by Ethical Committee
3. Confirmation of deposit of data
4. Verification by independent experts
5. Verification by Advisory Board Committee
6. Special regulations for imported materials
7. Approval also by regional ethical committees
8. Import licence required for non–registered products. New legislation in progress
9. Phase I: Not covered by current legislation
   Phase II: CTX application (clinical trial exemption) for 5 (or extended to 9) week trials. CTC application (clinical trial certificate) for 1 year + trials

Table 10. Toxicological testing requirements for pesticides (Provisional and final registration).

USA: Well defined testing requirements depending on proposed use. (Fed. Reg. 48, No 12, Jan. 18, 1983)
Europe: Testing requirements not defined. In general, the following tests are required.
Acute toxicity oral (rat, mouse), dermal (rat), inhalation (rat)*
Skin and eye irritation, single application (rabbit)
Skin sensitization (guinea pig)
28 d oral, 21–28 d dermal toxicty (rat)
3 m oral toxicity (rat, dog)
Mutagenicity studies
Teratogenicity(rat, rabbit)
24 m combined oral toxicity and oncogenicity (rat)*
18 m oncogenicity (mouse)*
12 m oral toxicity (dog)*
2 generation reproduction study (rat)*
Neurotoxicity study, hen, (for selected compounds)*

* Required for final registration.

DECISION MAKING PROCESSES

In the previous paragraphs, several examples were given showing differences in safety testing requirements in various countries. It should be mentioned, that the rule making and legislation process is continually going on in most countries and in supranational organizations. Thus, it is almost impossible to keep up with the everchanging situation of the regulatory climate in various countries.

It should also be noted that there exist remarkable differences in the assessment process of risk, based on the available toxicological data. The most glaring example is the "Delaney clause" contained in the US law regulating marketing of foods and drugs (9). It states that no food additive or color additive for use in foods may be approved for marketing, if it was shown to induce cancer in humans or animals. In all European countries, carcinogenicity studies of food additives are evaluated on a scientific basis, and marketing licences may be granted even if tumor incidence was increased in long–term rodent experiments.

But even in Europe, regulatory decisions based on the identical data may be different. Each country has its own set of standards, its own groups of outside experts and its own regulators. Thus, the registration process can become a slow, tedious, and often costly obstacle course. What is missing is a scientifically impeccable, supranational decision making body, consisting of experienced, independent and omniscient personalities who could govern the testing and approval process of all chemicals for all countries of the world. Until this utopic goal is reached, it is up to all people of good will to continue the efforts to harmonize testing guidelines and to develop generally acceptable procedures for evalaution of test results and risk assessment. The scientific community which has neither commercial obligations nor bureaucratic greed for power, is summoned to take a leading part in this important endeavour.

ACKNOWLEDGEMENTS

The author gratefully acknowledges the help of Prof. R. Bass, BGA, Berlin, Dr. R. Dixon, Sterling–Winthrop. Rensselaer, N.Y., Dr. W. Gfeller, Ciba–Geigy, Basel and Dr. Kämmereit, Byk Gulden, Konstanz.

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