TESTING OF CHEMICALS, SAFETY EVALUATION AND REGULATION AT EUROPEAN COMMUNITY LEVEL

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Abstract—Regulations regarding safety of chemicals are covered by the following main programmes:
— health and safety at work
— internal market and technical harmonization
— environmental and consumer protection.

The elaboration of draft Community legislation by the Commission for transmission to Council and the European Parliament requires an evaluation of the scientific data together with a determination of the technical possibilities and economic impact. Studies, scientific committees, national experts and tripartite advisory committees are used. For new chemicals premarketing testing is required for labelling. The testing scheme is described.

From the legislative point of view chemical safety is considered essentially in terms of six broad categories:
— air and water pollution and handing of toxic wastes,
— classification and labelling of dangerous chemicals and preparations,
— limitations of use of dangerous substances and preparations,
— occupational health and safety measures,
— prevention of major industrial chemical accidents,
— public health measures related to dangerous chemicals.

The classification and labelling of carcinogens and the regulation of the various facets of the use of lead will illustrate these regulatory procedures.

GENERAL APPROACH TO REGULATION IN THE FIELD OF HAZARDOUS TOXIC CHEMICALS

The community legislator has a wide choice of legal instruments for the promulgation of the Community legislation. These compromise regulations, directives, decisions, recommendations and opinions.

The main bodies involved in the decision making and follow-up process are:
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- Commission of the European Communities;
- Council of Ministers;
- European Parliament;
- Economic and Social Committee;
- European Court of Justice.

Figure 1 summarises the inter-relationship between these bodies, whose complexity may, to a certain extent, explain the lengthy decision making procedure. The development of a piece of Community legislation is both a complex and a time consuming task.

The common agreement of the public and of the authorities as to the importance of the health problems raised by the increasing use of chemicals in all Member States of the European Community has led in the last decade to the development of a number of Community actions programmes with a toxicology component fully within the spirit of the treaties.

Among these programmes one should mention:
- the Environmental research and action programmes;
- the Health Safety at Work action programmes;
- the Consumer Protection programmes;
- the Toxicology action programme for Health Protection.

These action programmes have already produced a significant body of knowledge based on the studies and research sponsored and coordinated at European Community level as well as a body of legislative measures specific to the European Community. A brief description of some of these legislative measures would be appropriate as these represent a unique feature of compulsory measures at the international level.

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— classification and labelling of dangerous chemicals and preparations;
— limitations of use of dangerous substances and preparations;
— occupational health and safety measures;
— prevention of major industrial chemical accidents;
— public health measures related to dangerous chemicals.

SPECIFIC REGULATORY APPROACH TO THE CLASSIFICATION AND LABELLING OF DANGEROUS CHEMICALS AND PREPARATIONS

In the 1960’s, the programme for the elimination of technical barriers to intra-community trade considered that there was a need for a unified approach towards the classification, packaging and labelling of dangerous substances, to facilitate trade and protect the public health.

The EEC labelling requirements are intended to provide a clear primary means by which all persons (workers as well as the public at large) handling or using substances or preparations are given essential information about the inherent dangers (safety and health) of certain such materials.

The classification of dangers as revised in the 6th Amendment of 1979 to the 1967 Council Directive (1), and the corresponding symbols where appropriate are given in Table I. In addition to the symbols the label must include standard sentences

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>LABELLING SYMBOL</th>
<th>CLASSIFICATION</th>
<th>LABELLING SYMBOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPLOSIVE</td>
<td>EXPLODING BOMB (E)</td>
<td>HARMFUL</td>
<td>ST. ANDREW'S CROSS (X)</td>
</tr>
<tr>
<td>OXIDIZING</td>
<td>FLAME OVER A CIRCLE (O)</td>
<td>CORROSIVE</td>
<td>SYMBOL SHOWING THE DAMAGING EFFECT OF AN ACID (C)</td>
</tr>
<tr>
<td>EXTREMELY FLAMMABLE</td>
<td>FLAME (F)</td>
<td>IRRITANT</td>
<td>ST. ANDREW'S CROSS (XI)</td>
</tr>
<tr>
<td>HIGHLY FLAMMABLE</td>
<td>FLAME (F)</td>
<td>DANGEROUS FOR THE ENVIRONMENT CARCINOGENIC</td>
<td></td>
</tr>
<tr>
<td>VERY TOXIC</td>
<td>SKULL AND CROSS-BONES (T)</td>
<td></td>
<td>TERATOGENIC</td>
</tr>
<tr>
<td>TOXIC</td>
<td>SKULL AND CROSS-BONES (T)</td>
<td></td>
<td>MUTAGENIC</td>
</tr>
</tbody>
</table>
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describing the nature of the special risks and giving safety advices. Typical risk phrases related to toxicity are: harmful in contact with skin; very toxic by inhalation; dangers of cumulative effects, etc... Typical safety phrases include: keep contents under water; when using do not smoke; take off immediately all contaminated clothing; etc...

Up to now close to a 1200 substances have been examined, classified and listed. However this number is very small in comparison to the existing substances, amongst which at least 40% would require classification under the meaning of the directive.

For new substances the 6th amendment requires the manufacturer or importer to submit a notification dossier to the competent authorities.

This dossier must include:

- a technical dossier supplying the information necessary to evaluate the risks which the new substance may entail for man and the environment. It should contain at least the information and results of the studies referred to in the so called base set which concerns physicochemical, toxicological and ecotoxicological tests; Table 2 shows the toxicity tests as foreseen in the base set.
- a declaration concerning the unfavourable effects of the substance in terms of the various uses envisaged;
- the proposed classification and labelling;
- the proposals for any recommended precautions relating to the use of the substance.

Table 2 Base set of toxicity for "new" chemicals

<table>
<thead>
<tr>
<th>1. ACUTE TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 LD 50 ORAL, INHALATION, CUTANEOUS,</td>
</tr>
<tr>
<td>Usually two routes of administration</td>
</tr>
<tr>
<td>Rats male and female</td>
</tr>
<tr>
<td>14 days observation</td>
</tr>
<tr>
<td>1.2 SKIN IRRITATION</td>
</tr>
<tr>
<td>Albino rabbit</td>
</tr>
<tr>
<td>1.3 EYE IRRITATION</td>
</tr>
<tr>
<td>Rabbit</td>
</tr>
<tr>
<td>1.4 SKIN SENSITIZATION</td>
</tr>
<tr>
<td>Guinea-Pig</td>
</tr>
<tr>
<td>2. SUB-ACUTE TOXICITY</td>
</tr>
<tr>
<td>28 day administration, usually oral</td>
</tr>
<tr>
<td>Rat preferably</td>
</tr>
<tr>
<td>3. MUTAGENICITY</td>
</tr>
<tr>
<td>Series of two tests</td>
</tr>
<tr>
<td>Bacteriological with &amp; without metabolic activation</td>
</tr>
<tr>
<td>Non-bacteriological</td>
</tr>
</tbody>
</table>

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It is clear that the results of these tests will allow not only a more appropriate classification of the substance if it presents dangers, and definition of these dangers, but will also serve as one of the sources of information for setting control requirements as well as hygiene and medical surveillance measures for workers exposed to these substances.

The directive provided also for additional toxicity testing requirements in relation with the results of toxicity testing in the base set, the uses known or foreseen and the quantity of the chemical put on the market.

The quantity related additional testing requirements are:

**At level 1** (10 T/Year per notifier or a total of 50 T)
- fertility study
- teratology
- sub-chronic and chronic toxicity
- additional mutagenesis studies-including screening for carcinogenesis.

**At level 2** (1000 T/Year per notifier or a total of 5000 T)
- chronic toxicity
- carcinogenicity study
- depending of the results at level 1
  - fertility study
  - teratology study
  - acute and sub acute study on a 2nd species
- toxicokinetic studies.

The directive foresees also that the tests carried out shall comply with the principles of good current laboratory practice. At Community level a proposal for a Council directive related to the application of good laboratories practice and the verification of their application for tests on chemical substances made by the Commission in 1985 (2) is currently in discussion at Council.

In a Commission Directive of 1984 (3) the methods for the determination of physico-chemical, toxicological, ecotoxicological properties have been laid down for the part corresponding to the "base set" on the same lines as agreed in OECD guidelines for testing of chemicals. Due to the mandatory aspect for testing at the base set level, there was a need to establish harmonized methods. When in the OECD guidelines several tests are proposed and considered equivalent, at Community level a selection had to be made indicating the preferred (reference) method to be applied. For example the OECD guideline 406 "Skin sensitization" considers any of seven methods as acceptable for testing this property. At Community level for skin sensitization the "reference" method is the Guinea Pig maximisation test (GPTM)-any alternative test, if used, has to be shown to give equivalent results and be justified.

The above approach should significantly contribute to improve the health protection of all those exposed to chemicals, workers in the first place. Unfortunately it is limited however to pure substance, while exposure most frequently occurs to
mixtures (or preparations).

From a scientific point of view, it is at present very difficult to transpose toxicological data from pure compounds to mixtures. Usually the additivity rule is used, which of course does not take into account synergisms and antagonisms. The additivity approach has been used in the 1973 directive on solvents (4). For example to determine if a preparation is to be classified and labelled as toxic or harmful, an empirical computation system has been set up based on a classification index for the toxic and harmful substances which may compose this preparation.

Recognizing the importance to develop an overall approach for the labelling of all preparations by the manufacturer a comprehensive proposal for a Directive has been submitted by the Commission to Council in 1985 (5) and is now actively under discussion.

**SCIENTIFIC EVALUATION AND LABELLING OF CARCINOGENS**


**Carcinogenic substances**

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

**Category 1**

Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

**Category 2**

Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

- appropriate long-term animal studies,
- other relevant information.

**Category 3**

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.

The following specific risk phrases apply:

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Categories 1 and 2:
R 45: May cause cancer
Category 3:
R 40: Possible risk of irreversible effects

The following classifications apply:
Categories 1 and 2: at least: Toxic
Category 3: Harmful

The complex scientific and administrative procedure for labelling carcinogenic substances is summarized in Figure 2.

![Figure 2 Procedure for labelling of carcinogens](image)

As a result of such a procedure the 7th Commission Directive 1986 (7) for the adaptation to technical progress of the 1967 Council Directive 27 substances or group of substances have been “may cause cancer” (Table 3).

<table>
<thead>
<tr>
<th>Substance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethylsulphate</td>
<td>Benzidine and salts</td>
</tr>
<tr>
<td>Diethylsulphate</td>
<td>Zinc chromate</td>
</tr>
<tr>
<td>Cadmium chloride</td>
<td>Calcium chromate</td>
</tr>
<tr>
<td>Benzene</td>
<td>Strontium chromate</td>
</tr>
<tr>
<td>1, 2-Dibromoethane</td>
<td>Chlorodimethylether</td>
</tr>
<tr>
<td>1, 2-Dibromo-3-chloropropane</td>
<td>5 Nitroacenaphthene</td>
</tr>
<tr>
<td>Epichlorhydrin</td>
<td>3, 3'-Dichloro-benzidine and salts</td>
</tr>
<tr>
<td>bis-Chloromethyl-ether</td>
<td>4-Aminobiphenyl and salts</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>N, N-Dimethylnitrosamine</td>
</tr>
<tr>
<td>2-Nitropropane</td>
<td>4, 4' Methylene bis (2-chloroaniline) and salts</td>
</tr>
<tr>
<td>2-Naphthylamine and salts</td>
<td>Methylaziridine</td>
</tr>
</tbody>
</table>

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OVERVIEW OF REGULATIONS ON LEAD AND ITS COMPOUNDS

The large number of directives that have been proposed by the Commission and adopted by the Council regarding lead cover:

- general assessment of the problem and information (biological monitoring and labelling)
- environmental limits (lead in air, surface waters)
- general product limits (drinking water, paints, cosmetics, petrol, animal feedstuff)
- specific population groups (occupational exposure)
- specific product oriented limits (children's toys)

These proposals and legislations are summarized in Table 4 with reference to the aims, main features, dates of application, etc (8).

<table>
<thead>
<tr>
<th>AIM OF LEGISLATION</th>
<th>DATE ADOPTED</th>
<th>MAIN FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead in ambient air</td>
<td>1982</td>
<td>2 ug/m3</td>
</tr>
<tr>
<td>Lead in surface waters set the abstraction of drinking water</td>
<td>1975</td>
<td>50 ug/l</td>
</tr>
<tr>
<td>Biological monitoring of the population for inorganic lead at work</td>
<td>1977</td>
<td>median blood lead 20 ug/ml</td>
</tr>
<tr>
<td>Inorganic lead at work</td>
<td>1982</td>
<td>150 ug/m3 air 70-80 ug/100 ml blood</td>
</tr>
<tr>
<td>Lead in petrol 1st</td>
<td>1978</td>
<td>0.15-0.40 g Pb/l in &quot;leaded&quot; petrol</td>
</tr>
<tr>
<td>Lead in petrol 2nd</td>
<td>1985</td>
<td>0.02-0.013 g Pb/l in &quot;unleaded&quot; petrol maxim. 0.15g Pb/l in &quot;leaded&quot; petrol benzene maximum 5 %</td>
</tr>
<tr>
<td>Drinking water</td>
<td>1980</td>
<td>50 ug/l (running water measures to be taken at levels exceeding 100 ug/l)</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Cosmetics</th>
<th>1976 July</th>
<th>lead and salts prohibited exception lead acetate allowed only in products for hair treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paints</td>
<td>1977</td>
<td>label: T-lead alkyls - 0.1 Xn-lead alkyls 0.01-0.1 % + special provision</td>
</tr>
<tr>
<td>Animal feedstuff</td>
<td>1974</td>
<td>i) straight feedingstuffs maximum 10 mg/kg except: phosphate maxim. 30 mg/kg yeast maxim. 5 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ii) complete feedingstuffs 5 mg/kg</td>
</tr>
<tr>
<td>Ceramics articles in contact with foodstuffs</td>
<td>1984</td>
<td>– category 1 Articles which cannot be filled or filled high: 25 mm: 0.8 mg/dm² – category 2 all other articles which can be filled: 4 mg/l – category 3 cooking ware: 1.5 mg/l</td>
</tr>
</tbody>
</table>

CONCLUSIONS

For the past twenty years and very progressively the necessary scientific and legislative instruments for the testing, safety evaluation and regulation of chemicals at European Community level have been elaborated.

Very recently, with the adoption of a Council resolution on an Action Programme on Toxicology for Health Protection, (9) another small step was taken. Through this programme toxicological methodology should be improved, and better use be made of Poison Centres to gather and assess clinical toxicological data.

A number of proposals are still pending such as the labelling of all preparations, the prohibition or limitation of use of certain chemicals at the workplace, exposure limits at the workplace, and others will be forthcoming.

REFERENCES

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(8) A. Berlin and M. Th. van der Venne, Regulating at European Community level to eliminate or reduce the health hazards due to lead Trace Metals in medicine (in press).

(9) Resolution of the Council and the representatives of the Governments of the member States, meeting within the Council, of 29 May 1986, on a programme of the European Communities on toxicology for health protection 86/C 184/01-Official Journal of the European Communities C 184 of 23. 07. 1986 p 1.

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