II

Acts whose publication is not obligatory

COMMISSION

COMMISSION DIRECTIVE

of 18 November 1987

adapting to technical progress for the ninth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances

(87/302/EEC)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,

Having regard to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (1), as amended for the sixth time by Directive 79/831/EEC (2), and in particular Article 19 thereof,

Whereas Article 3 (1) of Directive 67/548/EEC provides that the physico-chemical properties, toxicity and ecotoxicity of the substances and preparations shall be determined according to the methods specified in Annex V;

Whereas Article 3 (2) of Directive 67/548/EEC provides that the real or potential environmental hazard of a substance or preparation shall be assessed according to the characteristics set out in Annexes VII and VIII;

Whereas Annex V to the version introduced by Commission Directive 84/449/EEC (3) presently contains only those test methods corresponding to the characteristics detailed in Annex VII and it is necessary also to make available test methods corresponding to the characteristics detailed in Annex VIII;

Whereas the provisions of this Directive are in accordance with the opinion of the Committee for the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in Dangerous Substances and Preparations,

HAS ADOPTED THIS DIRECTIVE:

Article 1

The text of the Annex to this Directive is added to Annex V to Directive 67/548/EEC.

Article 2

Member States shall adopt and publish before 31 December 1988 the measures needed to comply with this Directive and shall immediately inform the Commission thereof. They shall apply those measures by 30 June 1989 at the latest.

Article 3

This Directive is addressed to the Member States.

Done at Brussels, 18 November 1987.

For the Commission
Stanley CLINTON DAVIS
Member of the Commission

(1) OJ No 196, 16. 8. 1967, p. 1/67.
(2) OJ No L 259, 15. 10. 1979, p. 10.
(3) OJ No L 251, 19. 9. 1984, p. 1.

ANNEX

The test methods described herein are for the determination of some of the toxicological and ecotoxicological properties listed in Annex VIII to Council Directive 79/831/EEC. Test methods appropriate to level 1 and level 2 of Annex VIII are described, but the tests are not subdivided as a function of the different levels.

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PART B: METHODS FOR THE DETERMINATION OF TOXICITY

GENERAL INTRODUCTION: PART B

LONG-TERM STUDIES

Sub-chronic, chronic and carcinogenicity studies

Characterization of the test substance and treatment mixture

The composition of the test substance, including major impurities, and its relevant physico-chemical properties, including stability, should be known prior to the initiation of any toxicity study.

The physico-chemical properties of the test substance provide important information for the selection of the route of administration, the design of sub-chronic, chronic or carcinogenicity studies and the handling and storage of the test substance.

Information on chemical structure and physico-chemical properties may also provide and indication of the absorption characteristics by the intended route of administration and the metabolic and tissue distribution possibilities. There may also be information on toxicokinetic parameters from preceding toxicity and toxicokinetic studies.

The development of an analytical method for qualitative and quantitative determination of the test substance (including major impurities when possible) in the dosing medium and biological material should precede the initiation of the study.

Experimental animals: selection of species and strain

Since it is necessary to treat animals for a major portion of their lifespan, the studies tend to be limited to easily maintained and relatively short-lived test species. It is highly desirable that the incidence of spontaneous disease and tumours in the strain of animal used, when kept under similar conditions, be known.

Strains should be well characterized and free from interfering congenital defects. The use of inbred strains, of F1 hybrids, has some advantages in this respect, but where sufficient background data are available on outbred strains, with animals derived from closed stocks, these are acceptable.

Animal care, diet and water supply

Animal tests and studies shall be conducted in accordance with national regulations and shall take into account humane principles and international developments in the field of animal welfare.

Stringent control of environmental conditions and proper animal care techniques are mandatory for meaningful results. Factors such as housing conditions, intercurrent disease, drug therapy, impurities in diet, air, water, and bedding, and general animal-care facilities can significantly influence the outcome of repeated dose studies. In general, the effect of chemical sterilants on the study should be known.

The diet should meet all the nutritional requirements of the species tested and should be free of impurities that might influence the outcome of the test. Rodents should be fed and watered *ad libitum*, with food replaced at least weekly. At present, three types of diet are utilized: conventional, synthetic, and various open formula diets.

Whichever diet is chosen, suppliers must ascertain by periodic monitoring the nutritive value and the level of contaminants in the basal diet and provide this information to the laboratory with each batch of feed. It is highly desirable that the effects of the dietary regimen on metabolism, as well as on the development of tumours and animal longevity, are known.

In addition, check analyses of the basal diet may be carried out by the testing laboratory for both food components and unintentional contaminants, including carcinogens. If this is done, the results of analyses should be retained and included in the final report on each test substance.

Common dietary constituents which are known to influence carcinogenesis (e.g. anti-oxidants, unsaturated fatty acids, selenium) should not be present in interfering concentrations. The potential impact of several common dietary contaminants upon carcinogenicity assessment requires that special attention is paid to the presence in the diet of pesticide residues, organochlorine compounds, polycyclic aromatic hydrocarbons, oestrogens, heavy metals, nitrosamines and mycotoxins.

When the test substance is administered in the water or food, stability tests are essential. Properly conducted stability and homogeneity tests, prior to the repeated dose studies, should be used to establish the frequency of diet preparation and monitoring required.

When diets are sterilized, the effects of such procedures on the test substance and dietary constituents should be know. Any appropriate adjustments should be carried out.

During carcinogenicity tests, investigators should be aware of potential contaminants in the water used. Water approved for human consumption is generally satisfactory and information on its composition should be available.

The concentration of a test substance in the diet may need to be adjusted as the animals grow in order to maintain a reasonably constant intake of test substance relative to body weight.

The nutritive value of control and test diets should be made as similar as possible. Thus the nutritive value of a test substance mixed in the diet needs to be considered. Experience suggests that up to 5 % of non-nutritive test substances in the diet is unlikely to interfere significantly with the nutritional value of the diet.

1. Inhalation studies

No limit test is specified because it has not been found possible to define a single inhalation exposure limit value.

2. Teratogenicity study

The test method is primarily directed to administration by the oral route. Alternatively, other routes may be used depending on the physical properties of the test substance or likely route of human exposure. In such cases, the test method should be suitably adapted taking into consideration the appropriate elements of the 28-day test methods.

3. Toxicokinetics

Toxicokinetic studies help in the interpretation and evaluation of toxicity data. These studies are intended to elucidate particular aspects of the toxicity of the chemical under test and the results may assist in the design of further toxicity studies. It is not envisaged that in every case all parameters will need to be determined. Only in rare cases will the whole sequence of toxicokinetic studies (absorption, excretion, distribution and metabolism) be necessary. For certain compounds, changes in this sequence may be advisable or a single-dose study may be sufficient.

Definitions

Toxicokinetics:	the study of the absorption, distribution, metabolism and excretion of test substances;
Absorption:	the process(es) by which an administered substance enters the body;
Excretion:	the process(es) by which the administered substance and/or its metabolites are removed from the body;
Distribution:	the process(es) by which the absorbed substance and/or its metabolites partition within the body;
Metabolism:	the process(es) by which the administered substances is structurally changed in the body by either enzymatic or non-enzymatic reactions.

4. Acute and sub-acute study in a second species

The purpose of a study in a second species is to complement the conclusions drawn from the first.

In the case of a study in a second species, the test method already described may be used or adapted for a smaller number of animals.