COMMISSION OF THE EUROPEAN COMMUNITIES

REPORTS
OF THE SCIENTIFIC COMMITTEE
FOR FOOD

Third series

1977

SCIENTIFIC COMMITTEE FOR FOOD

The Committee was established by Commission Decision 74/234/EEC of 16 April 1974 (OJ No L 136 of 20.5.1974 page 1) to advise it on any problem relating to the protection of the health and safety of persons arising from the consumption of food, and in particular the composition of food, processes which are liable to modify food, the use of food additives and other processing aids as well as the presence of contaminants.

The Members are independent persons, highly qualified in the fields associated with medicine, nutrition, toxicology, biology, chemistry, or other similar disciplines.

The opinions of the Committee are submitted to the Commission and as a rule are published. The present series relates to opinions given during the period indicated in the individual titles.

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Composition of the Scientific Committee for Food (1)

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(1) OJ No C 114 of 27.9.1974, p. 22

EXPLANATORY NOTE

The outline directive on materials and articles intended to come into contact with foodstuffs (1) provides the possibility of establishing, in specific directives applicable to certain groups of materials and articles, the list of substances the use of which is authorized (positive list).

The directive also provides the possibility for the inclusion in these lists of a new substance in accordance with procedures which include, among others, the intervention of the Scientific Committee for Food. As a consequence, the Committee was invited to make known the kind of information which it thought was necessary in order to give an opinion on the health aspects linked to the use of such a substance.

The information has been put together in the present publication.

(1) OJ No L 340 of 9 December 1976

TOXICOLOGICAL EVALUATION OF A SUBSTANCE FOR MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS

1 October 1976

1. INTRODUCTION

To assess whether a substance is harmful to man it is necessary to have information on its toxicity, on the quantity of the substance migrating into food and its daily intake by man.

To assess the toxicity of a chemical substance a number of biological tests may be undertaken. The programme of toxicity testing necessary for a specific substance depends on its physicochemical properties, its chemical structure, a knowledge of the toxicity of related compounds and on the quantity migrating into the food. Normally, the substance should be tested for long-term toxicity and the effects on reproduction and teratogenicity. However, under certain circumstances it may not be necessary to test the substance for long-term toxicity, for example where the chemical nature of the substance, the results of metabolic, biochemical or short-term studies, the degree of man's exposure to the substance, or other relevant information, suggest that it is not essential to insist on these long-term studies. The minimum requirements would be acute and 90-day tests in at least two relevant animal species using oral administration. Newer test systems (e.g. mutagenicity tests, in-vitro screening tests) are continuously being developed.

Generally, it is not practicable to describe exactly what tests should be carried out. Therefore, in the first instance, applicants are advised to consult the appropriate national authorities in order to agree an appropriate research programme for the toxicological evaluation of a substance which is to be submitted for acceptance as suitable to come into contact with foodstuffs.

2. GENERAL COMMENTS

Results must be prepared in such a way as to enable an evaluation. Reference to published material must be supported by documentary evidence, which may be in photocopy form. Depending on the substance under consideration, some of the information requested below may be unnecessary, while some may require further elaboration. If some of the information requested is not provided, the reason for its omission must explained.

3. IDENTITY

3.1. If the substance is a defined chemical compound indicate :

3.1.1. chemical name, (and/or chemical synonyms, abbreviations, trade names etc...);

3.1.2. molecular and structural formulae;

3.1.3. degree of purity, qualitative and quantitative data on the principal impurities.

3.2. If the substance is a mixture of two or more compounds, deal with each compound separately in accordance with 3.1. and give the proportions in the mixture.

3.3. If the substance cannot be clearly defined chemically, describe :

3.3.1. the compounds used in preparing the substance;

3.3.2. the production process, production controls, and reproducibility;

3.3.3. the method used to purify the substance;

3.3.4. all chemical products which may form during the process of manufacture.

4. PROPERTIES

Give :

4.1. Physical properties such as the physical state, melting point, boiling point, decomposition temperature, flash point, density, vapour pressure, and solubility in various solvents - particularly in liquids simulating the various types of foodstuff.

4.2. Chemical properties including stability on exposure to light, heat or water.

4.3. Information on any decomposition or transformation which the substance may undergo while the material or article is being manufactured, and an indication of the decomposition or transformation products which may be formed in the finished material or article, and the maximum temperature reached in the manufacturing process.

4.4. Information on the persistence of the substance in the finished material or article under environmental conditions and on its fate after the material or article has been submitted to waste disposal treatments.

5. USE

Give :

5.1. Type of material or article in which the substance is intended to be used.

5.2. Function which the substance is intended to perform in the material or article.

5.3. Justification for use of the substance (technical, economic, etc...)

5.4. Maximum percentage proposed in the formulation.

5.5. Maximum percentage which may remain in the material or article, when the amount, given under 5.4. is reduced by process as such as washing, purification, evaporation, etc.

5.6. Foodstuffs with which it will come into contact (general or specific use).

5.7. Contact conditions, with particular reference to temperature and length of contact (short or prolonged) and, if possible, the surface/weight of surface/volume ratio for the foodstuffs in contact.

6. INFORMATION ON USE OF THE SUBSTANCE IN OTHER COUNTRIES

State in which other countries, and under what conditions, the substance is authorised for use in contact with food. The official publication concerning the authorisation issued must be enclosed, as photocopy if necessary.

7. MIGRATION DATA

Give :

7.1. Details of the migration tests carried out (a reference will suffice for procedures laid down in any special directive on the material or article).

7.2. Results, including those from the specific determination of the migrant i.e. of the substance and if necessary, of its decomposition of transformation products.

7.3. Details of the analytical method or methods appropriate for determination of the migrant i.e. of the substance and, if necessary, of its decomposition or transformation products. The reproducibility and the limits of detection of the method(s) should be indicated.

8. TOXICOLOGICAL DATA

Give the details and the results of all the toxicity tests performed. Below is given a general outline of the toxicity tests which may be required in certain cases. (see INTRODUCTION).

8.1. Acute toxicity

Acute oral toxicity (LD50 and/or full acute toxicity observations) should be determined in at least two species of animal (preferably one non-rodent).

8.2. Ninety-day tests

In general, this test should be carried out using the oral route of administration and several dose levels. The experimental groups should contain an adequate number of animals of each sex and a control group should always be included. The dose levels should be chosen so as to determine a no-effect level and effect levels which would enable an evaluation to be made regarding dose-response relationship. All relevant biological data should be recorded at appropriate intervals and should cover, in particular, haematology, clinical chemistry including organ function tests, complete gross pathology and histopathology. If there is any evidence of specific toxicological effects, these should be investigated in detail and the mechanisms elucidated. The results should be presented in full detail, including statistical assessments of findings.

8.3. Long-term tests

Any long-term toxicity studies should extend over at least 90 per cent of the expected lifespan of the experimental animal strain used and should satisfy certain minimum requirements.

The number of animals in the various experimental and control groups must be sufficiently large to result in survival of an adequate number so as to allow for statistical evaluation. The investigations described in 8.2. should be carried out at appropriate intervals, and a thorough gross and histopathological examination of all animals must be done throughout and at the end of the experiment on a sufficient number of animals to allow for statistical assessment. If the study is concerned with carcinogenicity, particular attention must be paid to the time of appearance, incidence and character of any observed tumours.

Reproduction studies should extend over at least two filial generations and may be combined with long-term, teratogenicity and certain mutagenicity studies. Particular attention should be paid to observations on litters and their post-natal development and should include estimation of the usual indices of fertility, survival, growth and lactation.

Additional investigations with regard to mutagenicity, including *in-vitro* screening tests, and metabolism may contribute to the evaluation of the toxicity of the substance.

8.4. If it can be demonstrated that, as a result of its chemical conversion or physical properties, a substance will disappear completely during the manufacture of the material or article intended to come into contact with foodstuffs, the application for approval need not contain toxicological data relating to that substance.

It must however contain toxicological data relating to any decomposition or transformation products which remain in the manufactured product. It may also be necessary for the applicant to indicate an analytical method with an adequate limit of detection to determine the residues of the substance in the end product or in the migration test.

9. EVALUATION OF THE TOXICOLOGICAL DATA

Since toxicological data are generally obtained from animal experiments the data have to be extrapolated to man by established procedures. The latter involve choice of

an appropriate safety factor which takes into account variations in the weights of individuals, the existence of critical groups, the average quantity of food consumed per day, and the average quantity of food in contact with a standard surface area of material or article. From the data an estimate may be made of a toxicologically acceptable daily intake which is then compared with the intake estimated from migration data. Assessment of safety will depend on the relationship between these two quantities.

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