Environmental Health Criteria 70

PRINCIPLES FOR THE SAFETY ASSESSMENT OF FOOD ADDITIVES AND CONTAMINANTS IN FOOD

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The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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5.5.3 Toxicological versus physiological responses

When analysing a toxicological study and setting a no-observed-effect level, a distinction must be drawn between reversible changes that are due entirely to normal physiological processes or homeostasis-maintaining mechanisms, and to toxic responses themselves (section 5.1). Examples of the former include: laxative effects from osmotic or faecal overload, liver hypertrophy and microsomal enzyme induction from high doses of substances metabolized by the liver, decreased body weight gain or caecal enlargement from high levels of non-nutritive substances, alteration in renal weight that is directly related to the amount of water being processed by the kidney, and decreased growth rate and food consumption related to the dietary administration of an unpalatable substance. However, care must be taken in interpreting these changes, and they should not automatically be dismissed as being unimportant from a toxicological point of view. For example, microsomal enzyme induction in the liver may result in alterations in the metabolism of compounds unrelated to the administered substance, which could result in a toxic effect. A decrease in the rate of body-weight gain coupled with a corresponding reduction of food intake could be due to toxic anorexia, rather than a palatability defect.

The dose at which the effect occurs should be compared with the amount of the substance consumed by human beings. Thus, it would ordinarily be acceptable to permit the use of a substance that causes diarrhoea only at very high levels of consumption in rats, but the use of such a substance should be severely restricted or not permitted if it causes diarrhoea at normal levels of consumption in human beings. Sometimes, physiological adaptation may progress through overload to frank toxicity.

Further studies are indicated in situations in which it is difficult to draw a clear distinction between a toxic and a physiological response. Special studies such as paired feeding, caloric balance comparisons between food consumption and body-weight gain, or, in the case of reproduction studies, cross fostering, can be performed to decide issues such as reduced food intake and reduced body-weight gain related to unpalatable test substances. Metabolic and pharmacokinetic studies may be of use in providing information on the distribution of the test compound and its metabolites or the dose at which a change in metabolism occurs.