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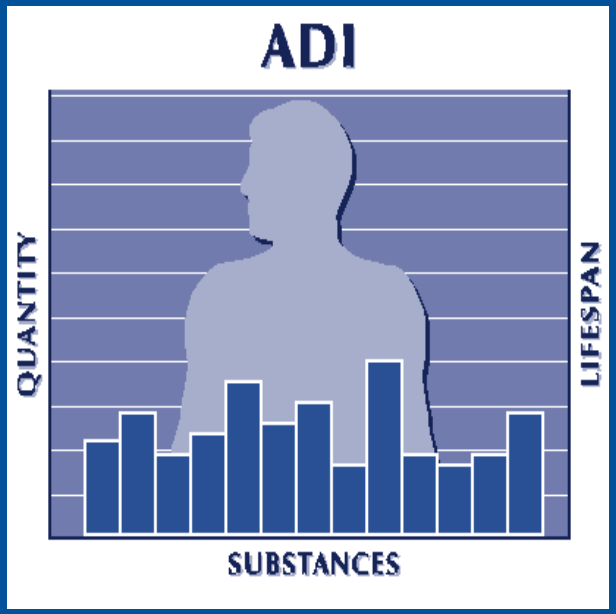

THE ACCEPTABLE DAILY INTAKE

A TOOL FOR ENSURING FOOD SAFETY

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ILSI EUROPE CONCISE MONOGRAPHS

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FOREWORD

The Acceptable Daily Intake is an estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk. (Environmental Health Criteria No. 70, JECFA 1987)

The concept of the Acceptable Daily Intake, the ADI, is internationally accepted today as the basis for estimation of safety of food additives and pesticides, for evaluation of contaminants and by this, for legislation in the area of food and drinking water.

The public concerns for safety of foodstuffs has led to a requirement for more transparency in the expert evaluations of chemicals in relation to human health. The ADI concept is an important background for safety assessment of ingredients in food. Understanding the ADI concept will improve the transparency and the confidence in the evaluations.

ILSI Europe's ADI Task Force initiated the current Concise Monograph on the Acceptable Daily Intake, for describing this "Tool for Ensuring Food Safety" generally. The content of the document includes science presented during workshops arranged by ILSI Europe on "Scientific Evaluation of the Safety Factor for the Acceptable Daily Intake" (1992), "Applicability of the Acceptable Daily Intake (ADI) to Infants and Children" (1997) and "The Significance of Excursions of Intake above the Acceptable Daily Intake (ADI)" (1998).

The monograph gives a historical view on the development of the concept of the ADI and why it is needed. It explains the use of the ADI for approval of food additives, pesticides and veterinary drugs within the European Union and the worldwide perspectives. The criteria for establishing an ADI and current test methods are covered in individual chapters. The derivation of the ADI and the use of safety factors is an important part of the monograph. For use of the ADI in risk assessment, intake information is needed. Methods for consumption studies and intake assessment are discussed in a chapter in this monograph. The last chapters provide an overview of applicability of the ADI to subgroups such as infants and children, and of the significance of intake at levels above the ADI.

The monograph is intended as a resource for regulatory authorities, health professionals and the many individuals actively involved in the debate on food safety.

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WHY WE NEED THE ADI

History

Throughout the twentieth century there has been an increasing trend towards the use of stored and processed foods. Initially this was a response to industrialisation and the need to provide food for large numbers of people living in cities. More recently, the consumer has come to expect access to a wide variety of foodstuffs throughout the year, without the restrictions imposed by seasonal and regional availability, and there is increasing reliance on convenience and fast foods. The processes involved in producing and storing foods frequently require the addition of chemicals (either natural or man-made) to improve the safety (microbiological safety) or to preserve nutritional quality. An additional benefit is increased palatability and attractiveness of foodstuffs to the consumer. Clearly the safety of such chemicals has to be assured and their use controlled in order to avoid harmful effects. Box 1 summarises the key events leading to the development of current legislation and regulatory requirements relating to the safety of chemicals in food.

In a resolution of the 1953 World Health Assembly, Government Delegates expressed "concern about the increasing use of various chemical substances in the food industry in the last few decades". In 1955, this concern led to the establishment of the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organisation of the United Nations (FAO) and the World Health Organisation (WHO). The JECFA is an independent scientific committee composed of scientists who serve in their individual capacities as experts and not as representatives of their governments or employers. Food additives were initially defined as "non-nutritive substances added intentionally to food, generally in small quantities, to improve its appearance, flavour, texture or storage properties". However, the terms of reference of JECFA were soon broadened to include substances introduced into food unintentionally, and some nutritive substances consumed in relatively high amounts (see Table 1). In order to provide a sound scientific basis for its reviews of food additives, the JECFA formulated general principles for the justifiable use of additives, and the toxicological evaluation by scientific experts and guidance on the conduct of toxicological studies.

TABLE 1

Examples of the range of substances reviewed by expert committees to ensure food safety

Food Additives[a]	Agricultural/ veterinary residues[a]	Contaminants[b]
Anticaking agents	Feed additives	Aerosol propellants
Antioxidants	Pesticides	Components of packaging materials
Bulk sweeteners	Veterinary drugs	Growth promoters
Colours		Metals
Emulsifiers		Mycotoxins
Flavouring agents		Solvents used in food processing
Intense sweeteners		
Preservatives		
Stabilisers		

[a] Acceptable Daily Intake is applied.

[b] Tolerable Intake is applied in EU, the term reference dose (RfD) is used in the USA.

BOX 1

Key events in the development of food safety standards

early 1900s: Food trade associations attempt to facilitate world trade through the use of harmonised standards.

1927: The US Bureau of Chemistry is reorganised into two separate entities. Regulatory functions are located in the Food, Drug, and Insecticide Administration, and nonregulatory research is located in the Bureau of Chemistry and Soils.

1930: The name of the Food, Drug, and Insecticide Administration is shortened to Food and Drug Administration (FDA) under an agricultural appropriations act.

1945: FAO is founded, with responsibilities covering nutrition and associated international food standards.

1948: WHO is founded, with a mandate to establish food standards.

1949: FDA publishes Guidance to Industry for the first time. This guidance, "Procedures for the Appraisal of the Toxicity of Chemicals in Food", came to be known as the "black book".

1950: Joint FAO/WHO expert meetings begin on nutrition, food additives and related areas.

1953: World Health Assembly states that the widening use of chemicals in the food industry presents a new public health problem that needs attention.

1954: Lehman and Fitzhugh of the FDA propose 100-fold margin of safety.

1954-1958: Austria pursues a regional food code, the Codex Alimentarius Europaeus.

1955: JECFA is established.

1958: Food Additives Amendment is enacted in the USA, requiring manufacturers of new food additives to establish safety. The Delaney proviso prohibits the approval of any food additive shown to induce cancer in humans or animals.

FDA publishes in the Federal Register the first list of Substances Generally Recognized As Safe (GRAS). The list contains nearly 200 substances.

1960: First FAO Regional Conference for Europe endorses the desirability of international agreement on minimum food standards.

1960: Color Additive Amendment is enacted in the USA, requiring manufacturers to establish the safety of color additives in foods, drugs and cosmetics. The Delaney proviso prohibits the approval of any color additive shown to induce cancer in humans or animals.

1961: Council of the Codex Alimentarius Europæus adopts a resolution proposing that its work on food standards be taken over by FAO and WHO.

1961: Codex Alimentarius is established by FAO with support of WHO, ECE and OECD.

1961: JMPR is established.

1962: Codex Alimentarius Commission is asked to implement a joint FAO/WHO food standards programme and to create the Codex Alimentarius.

1963: World Health Assembly approves establishment of the Joint FAO/WHO Programme on Food Standards and adopts the statutes of the Codex Alimentarius Commission.

1970: US Environmental Protection Agency is established and takes over FDA program for setting pesticide tolerances.

1974: EU Scientific Committee for Food (SCF) is established.

1982: FDA publishes the first "Redbook" (successor to the 1949 "black book", officially known as "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives".

1985: United Nations General Assembly recommends Governments "should support and, as far as possible, adopt standards from the .... Codex Alimentarius".

1987: WHO publishes Environmental Health Criteria 70: Principles for the Safety Assessment of Food Additives and Contaminants in Food.

1991: FAO/WHO Conference on Food Standards, Chemicals in Food and Food Trade (in cooperation with GATT) agreed that "the process of harmonising national food regulations to bring them into line with international standards and recommendations .... needed to be accelerated".

1992: FDA publishes draft of "Redbook II".

1995: WTO begins operation; its Agreement on Sanitary and Phytosanitary Measures specifies that member countries should base their food safety standards on those of the Codex Alimentarius.

1997: Following reorganisation of the European Commission's Scientific Committees, the importance of food safety is confirmed by reconstitution of the SCF (with the slightly amended name of the Scientific Committee on Food).

BOX 2

Body weight scaling

In comparing doses or intakes between animals and people, or between people of different sizes, it is necessary to use a scaling factor.

A number of different methods have been proposed, but the preferred one is to relate the amount of substance ingested to the body weight.
(e.g. mg/kg body weight).

Within this monograph, this method is applied to the:

- Dose levels used in animal studies
- Intake of additives
- Intake of foodstuffs
- The ADI

Also in the 1950s, similar concerns were raised in the US Food and Drug Administration (FDA) and the Food Protection Committee of the National Research Council, leading to recommendations on evaluating the safety of food chemicals. The proposal by Lehman and Fitzhugh of the FDA of particular note was for the use of a "100-fold margin of safety" between the maximum safe dosage in long term animal feeding studies and the maximum intake of the chemical from the total human diet.

Based upon the safety margin approach of Lehman and Fitzhugh, the JECFA developed the concept of the Acceptable Daily Intake – the **"ADI"**. This was defined as **"an estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk"**. The amount is expressed in proportion to the body weight, in order to allow for differences in body weight between test animals and humans, and for the variability in human size (e.g. children compared with adults) (see Box 2). It relates to daily ingestion, because accepted additives should not accumulate in the body. It is based upon scientific judgement of all facts known at the time of evaluation in order to define a limit, below which no harmful effects would be expected. More simply, it may be defined as an intake that is believed to be "without appreciable risk".

A number of leading scientists from around the world were involved in the discussions leading to the establishment of the JECFA and its *modus operandi*, but it is generally agreed that Professor René Truhaut (see photo) was the most influential. He was present at all the early meetings and is credited with being the father of the ADI.

Professor René Truhaut

The value of defining procedures for establishing safe levels of chemicals in food was soon recognised. In addition to the potential health benefits, the harmonisation of procedures for food standards has economic benefits in terms of removing barriers to international trade, which was also an important issue for the FAO in the 1950s. In 1960, the first FAO Regional Conference for Europe recorded "the desirability of international agreement on minimum food standards and related questions (including labelling requirements,

methods of analysis, etc.) … as an important means of protecting the consumer's health, of ensuring quality and of reducing trade barriers, particularly in the rapidly integrating market of Europe". Over the following year, the FAO entered into discussions with the WHO, the Economic Commission for Europe (ECE), the Organisation for Economic Co-operation and Development (OECD) and the Council of the *Codex Alimentarius Europæus* resulting in international consensus and establishment of the Codex Alimentarius Commission in 1961.

The ADI concept was adopted by the Joint FAO / WHO Meeting on Pesticide Residues (JMPR), an independent scientific expert committee like the JECFA, and similar approaches were taken by other bodies, and for other types of chemical. In the United States, the FDA also adopted the ADI approach, and related methods are used by the US Environmental Protection Agency (EPA) for contaminants, although the term ADI is replaced in EPA assessments by Reference Dose **(RfD)**.

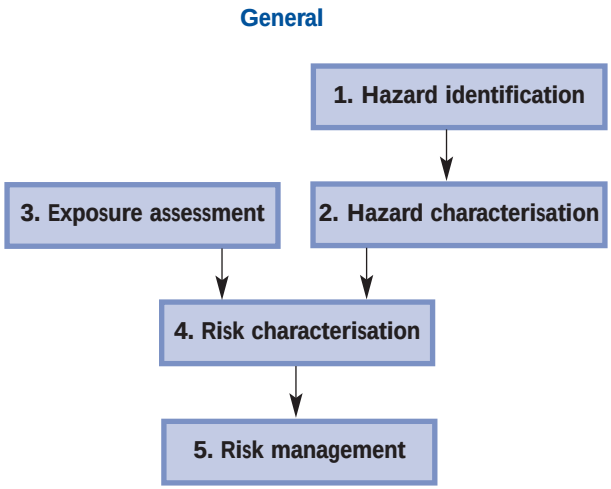
Food additives and contaminants

Regulatory authorities distinguish additives and residues from contaminants. Additives are added intentionally in order to produce some desired technical effect on the food, are approved onto a "positive list" and can readily be controlled. Similarly, pesticides and veterinary products have benefits in food production, and it is possible to control the amount of residue that persists from the crop or animal into the food we consume. In contrast, chemical contaminants are unwanted, but may be unavoidable. Therefore the levels of contaminants that are not expected to produce harmful effects are designated as tolerable (i.e. permissible) rather than acceptable.

The physical properties that lead to persistence of a chemical in the environment, resulting in contamination of food, are also likely to result in the chemical being more persistent in the human body than is considered acceptable for food additives. This means that contaminants may accumulate in the body with continued ingestion, and a longer reference period is considered necessary. In addition, the evaluation is considered to be tentative because of the paucity of reliable data on the consequences of human exposure at the levels anticipated to occur from food, and consequently the term Provisional Tolerable Weekly Intake **(PTWI)** is used. For contaminants of natural occurrence known not to accumulate in the body, JECFA establishes Provisional Maximum Tolerable Daily Intakes **(PMTDI)**. This category may include trace elements, such as iodine, that are essential nutrients as well as unavoidable food constituents. In such cases a range is indicated, with the lower value corresponding to the level of essentiality. Other expert committees and regulatory bodies may use the term Tolerable Daily Intake **(TDI)** for contaminants. Whilst the processes for evaluation of additives and contaminants are similar, the focus of this monograph is on the ADI, and therefore tolerable intakes are not considered further.

The risk assessment / risk management process is viewed as a number of separate steps, as illustrated in Figure 1. For food additives, the first two steps of hazard identification and hazard characterisation culminate in determination of the ADI. Derivation of the ADI is based upon scientific understanding of the toxicity of a food additive based on data from studies in animals and humans with the incorporation of a safety factor. The use of the safety factor illustrates the precautionary approach taken to food safety. When first introduced, the safety factor did not have a clear scientific rationale.

FIGURE 1
The risk assessment/risk management process for food additives



Specific steps for food additives

1. A wide range of tests to define the potential for harm (irrespective of dose) at the different stages of the life cycle.
2. Identification of the most important adverse effect(s) and analysis of the dose-response to define a level that is without effect.
   Consideration of inter-species differences and human variability, and the completeness of the database. Estimation of possible ADI.
3. Calculation of the potential daily intake based on the uses applied for, and the potential use levels.
4. Comparison of the potential daily intake with the ADI.
5. Recommendation of approved uses and use levels which ensure that the potential daily intake is less than the ADI.

However, there are no known incidences of public health problems arising from additives used within the ADI, and recent studies have provided scientific support for its value (as will be discussed later in this monograph). The ADI is therefore considered a valuable regulatory tool. The subsequent stages of the risk assessment and risk management processes take into account possible intake levels in different types of food in order to establish permissible use levels and apply them under national regulations.

PRINCIPLES – HOW THE ADI IS USED

Approval of food additives in the European Union

Within the European Union, a legislative framework has been established to allow the introduction of food safety standards either for the EU, or for individual member states, as shown in Figure 2.

EU-wide approval requires a safety evaluation by the Scientific Committee on Food (SCF), which was established by the Commission in 1974 to provide advice on any problem relating to health and safety aspects of food consumption, particularly on nutritional, hygienic and toxicological issues. The SCF evaluates a dossier of information provided by the manufacturers of a proposed new food additive, including toxicity data and details of intended usage. If satisfied with the safety data, the committee will establish an ADI. Legislation based on this advice is developed by the European Commission for presentation to the European Council of Ministers and to the European Parliament. The end result is an EC directive which requires all Member States to make the necessary changes to their national legislation.

Alternatively, the manufacturer may apply for national authorisation in one or more of the Member States, for an interim period, whilst applying for EU approval. In this instance, the application is reviewed by national expert committees, following similar procedures to those used by the SCF. If an ADI is established, the additive may be approved for marketing within that Member State for a period of two years whilst an application is made to the EU. The application is then considered by the SCF and, if approved, the additive is subsequently incorporated into an EU directive. If the application is not accepted by the SCF, the additive must be withdrawn.

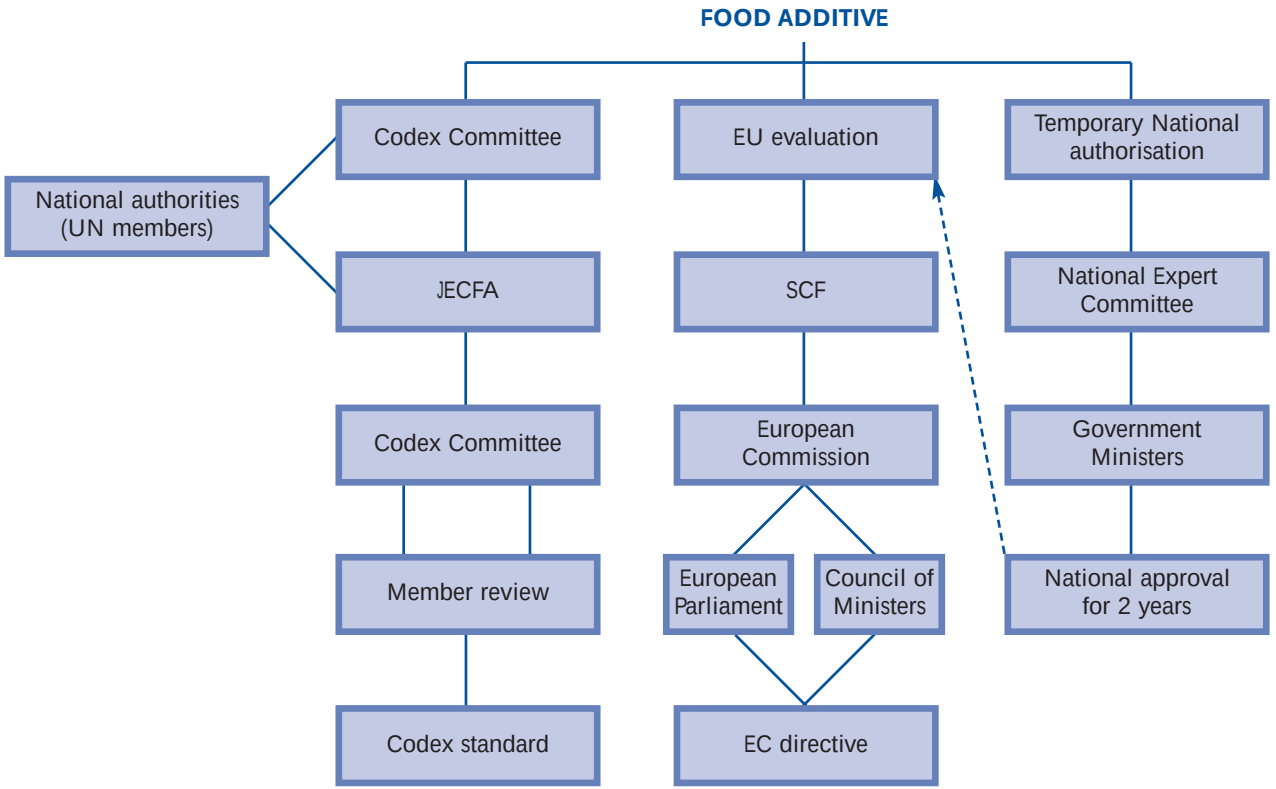
Legislation relating to approved food additives contains the following types of information:

- positive lists of permitted additives, including technical specifications such as purity;
- particular technological purposes for which the additives may be used;
- restrictions, such as maximum use levels in food.

Pesticides and veterinary drugs

The approach for residues of pesticides and veterinary drugs in food is similar to that for food additives. However, since pesticides are designed to be toxic to the pest species and veterinary drugs are intended to have pharmacological activity, it is also likely that they will be more toxic to mammalian species than most food additives. However, they are considered to be a necessary component of safe food production and therefore they are allocated an ADI rather than a tolerable intake. For pesticide residues, a Maximum Residue Level **(MRL)** is established by national regulatory agencies based upon the recommendations of JMPR and good agricultural practices, which are designed to ensure that pesticide residues in foods are maintained as low as is practicably possible. During the approval process the potential intake of residues can be compared with the ADI, taking into account the maximum amounts of relevant foods that a person would eat in a day. For residues of veterinary medicine and livestock feed additives, an MRL is derived by back-calculation from the ADI taking into account the maximum amounts of meat and dairy products that would be consumed per day.

FIGURE 2
Current framework for approval of a new food additive



Codex standards

As already noted, harmonisation of food standards supports both consumer health and international trade. Together these two factors have provided a compelling impetus for an increasing number of countries to align their food safety standards. The Codex Alimentarius Commission is responsible for making proposals to the FAO and WHO on all matters pertaining to implementation of the Joint FAO / WHO Food Standards Programme, which includes preparation of draft standards, guiding them through appropriate regulatory organisations and publishing them in the Codex Alimentarius. Membership of the Codex currently numbers 160 and is open to any country which is a member of the FAO or WHO.

In order to facilitate its activities, the Codex Alimentarius Commission has established a number of committees, including the Codex Committee on Food Additives and Contaminants (CCFAC). The CCFAC is responsible for identifying food additives and contaminants that should receive priority evaluation and refers them to JECFA. It is subsequently responsible for incorporation of JECFA's recommendations into Codex standards (see Figure 2). Thus the Codex committees are able to represent national interests, but the scientific evaluations are conducted by independent expert committees.

Once adopted by the Codex Commission, a *Codex standard* is added to the Codex Alimentarius. Permitted use levels will take JECFA assessments into account. The Codex will adopt standards only on those additives that have been cleared toxicologically by JECFA, and standards are reviewed in the light of new JECFA evaluations.

The Codex Alimentarius provides internationally agreed guidelines for food standards but does not have legislative power. A United Nations Resolution of 1985 advised that *"Governments should take into account the need of all consumers for food security and should support and, as far as possible, adopt standards from the ..... Codex Alimentarius"*. Many of the developed countries had their own established procedures for setting food safety standards. Greater importance was conferred on the Codex standards with the establishment of the World Trade Organisation (WTO) in 1995. Membership of the WTO requires countries to comply with the agreements. In particular, the Agreement on Sanitary and Phytosanitary Measures specifies that member countries should base their food safety standards on those of the Codex Alimentarius. It also requires the use of "risk assessment techniques developed by the relevant international organisations".

OVERALL CRITERIA FOR ESTABLISHING AN ADI

The dose-response relationship

The basic concept underlying any chemical risk assessment is the dose-response relationship. As described by Paracelsus nearly 500 years ago, "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy". This means that any chemical substance is likely to produce some form(s) of harmful effect, if taken in sufficient quantity. Experts refer to a potential harmful effect as a **hazard** associated with that substance. The Codex definition of hazard is "a biological, chemical or physical agent with the potential to cause an adverse health effect". Whilst this may be appropriate with respect to pathogenic organisms, chemical substances may be associated with a number of different adverse health effects, not all of which would necessarily be expressed in a specific exposure scenario. Therefore experts dealing with chemical substances prefer to define the potential health effects as individual hazards which need to be considered separately during the evaluation.

The likelihood or **risk** of that hazard actually occurring in humans is dependent upon the quantity of chemical encountered or taken into the body, i.e. the **exposure**. The hazard is an inherent property of a chemical substance, but if there is no exposure, then there is no risk that anyone will suffer as a result of that hazard.

Risk assessment is the process of determining whether a particular hazard will be expressed at a given exposure level, duration and timing within the life cycle, and if so the magnitude of any risk is estimated. Risk management may involve attempting to reduce the risk by reducing the exposure.

Derivation of an ADI is a specific form of risk assessment because it defines exposure limits below which no harmful effects are expected to occur. It assumes, based upon our current understanding of mechanisms of toxicity, that there is a **threshold** for most types of toxic effect. A threshold is a level of intake below which no effect is produced, either because the substance has had no effect or because the body's homeostatic mechanisms have reversed any changes caused.

There is a limited number of effects which theoretically may result from damage to a single cell, and therefore a precautionary approach does not allow us to assume a threshold, even though homeostatic processes and repair mechanisms may be effective at low exposure. The potential to cause cancer by means of damage to the DNA is the main example of a non-threshold effect. Accepted regulatory procedure is to assume that there is no safe level for such substances, and they are not considered to be suitable for deliberate addition to food. There is much debate amongst scientists and regulatory bodies on how to establish tolerable levels of DNA-damaging contaminants if they cannot be completely avoided (for example mycotoxins such as aflatoxin), but they would not be allocated an ADI and are not the subject of this monograph.

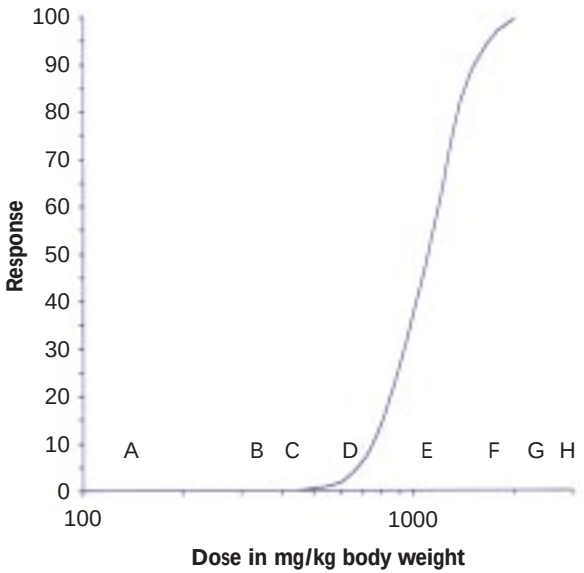
Table 2 gives examples of the different types of hazard, or effect, that may be associated with chemical toxicity. The objective of toxicity testing is to establish which type(s) of effect a particular substance may cause, and the relationship between the dose (or intake) and the occurrence of that effect. Figure 3 shows the curve of a typical dose-response relationship, which is generally produced in animal studies but is assumed to be equally valid for the human population. A similar curve is produced whether considering the frequency of an all-or-nothing response, such as death, or a continuously variable response, such as the severity of effect. No toxicity is seen at the lowest doses (A to C in the figure). Point C represents the **"threshold"** between dose levels that have no effect and those that do. For the frequency of response, as the dose is increased (C to D), a small number of individuals may be affected, representing the most vulnerable in the group. As the dose is increased further (D to H) the majority, and eventually all, of the exposed population will be affected. Alternatively for a variable response, the severity of response increases as the dose increases.

TABLE 2

Examples of types of adverse effect

Type of toxicity	Adverse effect
Functional changes	e.g. Reduced weight gain, laxation
Morphological changes (other than cancer)	e.g. Organ enlargement, pathological abnormalities
Mutagenicity	Heritable changes in DNA, genes and chromosomes, with the potential to cause cancer or fetal abnormalities
Carcinogenicity	Cancer
Immunotoxicity	Sensitisation (leading to hypersensitivity or allergy)
	Depression of the immune system (leading to increased susceptibility to infection)
Neurotoxicity	Behavioural changes, deafness, tinnitis, etc.
Reproductive toxicity	Impaired fertility
	Embryotoxicity (spontaneous abortion)
	Teratogenicity (fetal deformities)
	Other developmental effects

FIGURE 3
Typical dose-response relationship



Toxicity studies in animals aim to use a small number of doses distributed over the range of this curve, such that the highest and intermediate dose will be sufficient to establish the types of effect (hazard) generated by a particular substance. Some chemicals cause more than one of the different types of toxicity shown in Table 2, but normally one effect will occur at lower doses than the others. This effect is referred to as the **critical effect**.

In order to calculate an ADI using the data from toxicity studies, the lowest dose should ideally result in no effects under the conditions of the particular study. Thus the dose at point C in Figure 3 may be termed as the No Observed Effect Level (**NOEL**). Observed effects are referred to because assumptions cannot be made about effects not detectable by the methods used. Some effects observed in toxicity studies may represent adaptive responses with no implications for the health status of the animal and would generally not be used as the basis for establishing an ADI. Effects that are considered to result in harm to the animal are referred to as "adverse", and therefore some expert committees use the expression No Observed Adverse Effect Level (**NOAEL**). Deciding whether a particular effect is adverse depends on the specific circumstances for each evaluation and is an important aspect of the judgement applied by expert committees. For example, decreased body weight gain accompanied by decreased food consumption may be caused by high levels of chemical substance in the chow reducing palatability, i.e. not an adverse health effect. Alternatively, it could be a reflection of generalised poor health status of the animals, in which case it would be considered adverse and, in the absence of other symptoms, would be used as the basis for setting the ADI.

It is important to realise that the NOAEL is not an inherent property of a substance; it is an experimental observation (the value of which is dependent on the way in which a toxicity study is designed) and it does not necessarily coincide with the threshold dose. If doses C, E and G were selected for a study on the chemical with dose response shown in Figure 3, the conclusion would obviously be that C was the NOAEL. However, if the doses were B, D and F, then a lower value (i.e. dose B) would be reported as the NOAEL. The interval between dose groups is frequently quite large, and therefore it is possible that the NOAEL identified by a study could be considerably lower than the threshold. Alternatively, if the doses were D, F and H, the study would not identify a NOAEL, and dose D would be referred to as the Lowest Observed Adverse Effect Level (**LOAEL**). This lack of precision over identification of the NOAEL is the

first of a number of uncertainties involved in the risk assessment process. A LOAEL may be used for the risk assessment of contaminants but would not be used as the basis for the calculation of an ADI and approval for a food additive. For a food additive, or other compounds approved onto a positive list, the manufacturers would be required to repeat the study at lower doses in order to define the NOAEL.

Variation and uncertainty

Modern toxicity studies are conducted in laboratory animals (mostly rodents) which have been bred specifically for the purpose. The animals should be of a defined genetic strain, free of infectious agents and maintained under strict conditions that control all aspects of their care, hygiene, caging and bedding, diet, drinking water purity, temperature, humidity, light cycles and atmospheric conditions. The environmental and genetic controls mean that the individual animals used in a toxicity test are very similar to each other and therefore respond to toxic insult in a relatively homogeneous manner. This reduces the background variability and therefore increases the sensitivity of the study to identify effects at low doses. This is necessary both for the ethical and legal requirements to minimise numbers of animals used in toxicity testing, and to ensure the highest standards of quality for toxicity studies. Statistically significant differences between effects of different doses can be seen using groups of small numbers of animals. With detailed documentary evidence of how the animals are treated, and the ensuing effects, we can have confidence that the only differences between groups of animals in a toxicity study relate to the dose of the substance that they received, i.e. to the exposure. Hence any observed effects can readily be attributed to that exposure.

In contrast there is wide variability within the human population compared with test animal species.

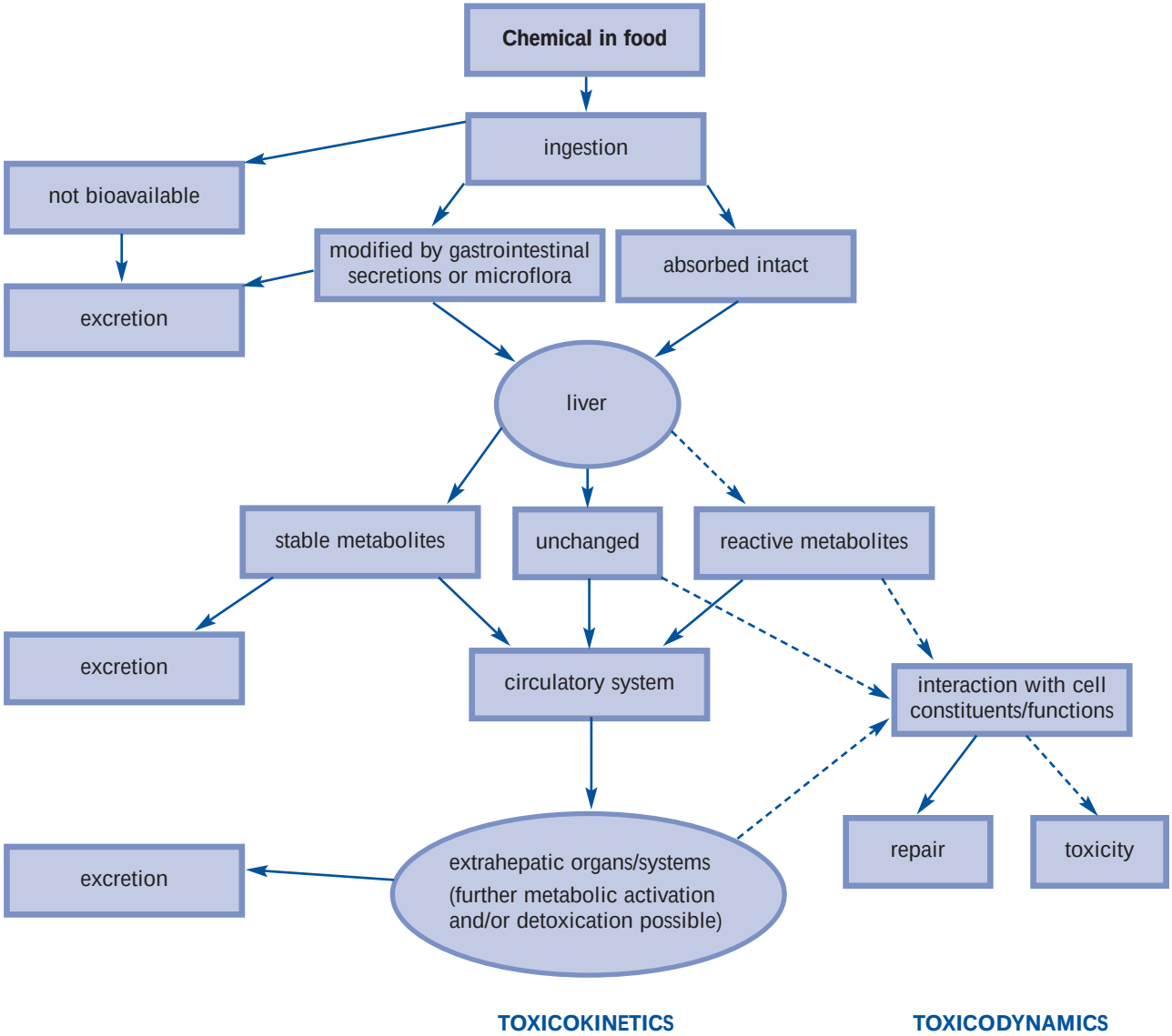
The stages leading to possible toxicity of an ingested substance are shown in Figure 4. Susceptibility to toxicity may be influenced by many factors acting on any of these different stages. Some of the modifying factors are internal to the individual, including genetic differences, gender, age, hormonal status and disease status. External factors include components of the diet and substances that humans are exposed to from the environment (shown in Table 3), which may vary considerably at different times for one individual.

TABLE 3

External factors that may influence susceptibility to toxicity

Dietary factors	Environmental factors
Alcohol	Drugs of abuse
Carbohydrate	Heavy metals
Essential elements	Industrial pollutants
Fat	Pesticides
Protein	Petroleum products
Pyrolysis products (formed during cooking)	Pharmaceuticals
Trace elements	Pyrolysis products (as pollutants)
Vitamins	Tobacco smoke

FIGURE 4
The fate of an ingested chemical in the body, possibly leading to toxicity



Dotted arrows indicate pathways leading to toxicity

Therefore, when attempting to use information from animal tests to predict risk to people, we need to be aware of two major categories of variability:

i. the differences between the animal species used in the toxicity study and *Homo sapiens* in general, i.e. **inter-species variability**;

ii. the variability in sensitivity that might be expected amongst the human population, i.e. **inter-individual variability** (also referred to as **intra-species variability**).

Within each of these categories, it is possible to consider two major causes of variability:

a. the fate of a chemical in the body, i.e. how a chemical is absorbed into the body, distributed around it, modified to different chemical structures (known as metabolism or biotransformation) and eliminated from the body. These processes are referred to as **toxicokinetics**.

b. the effects of the chemical on the body, leading to a toxic response with possible repair and regeneration. These processes are referred to as **toxicodynamics**.

These sources of variability form a major component of the uncertainties involved in establishing ADIs (see Table 4). Scientific understanding of toxicokinetics and toxicodynamics is increasing rapidly, but detailed knowledge is limited to very few chemical substances and is not comprehensive even for these.

As already noted, toxicity studies are designed to produce measurable effects at the highest doses. In general, food additives are selected for low toxicity and are therefore relatively innocuous. This means that very large amounts may have to be administered to animals in order to produce an effect. The additive may be present at up to 5% by weight of the animal diet, and at such concentrations it is possible that adverse effects could arise from nutritional imbalance. In contrast, additives generally form an extremely small proportion of the total amount of food ingested in humans and are consumed in small amounts. However, without detailed information on the mechanism of action of a particular substance, an assumption has to be made that the type of toxicity seen at high doses in the animal studies could theoretically occur at lower levels of intake in the most sensitive individuals of the human population.

The need for the safety factor

The above text describes a number of uncertainties involved in extrapolating from a dose of a chemical that has no effect in animals to a level of intake that will be safe for people, as summarised in Table 4. Because of these uncertainties, it is considered necessary to take a cautious approach which assumes that people may be more sensitive to toxicity than laboratory animals, and therefore a margin of safety must be allowed between

TABLE 4

Sources of uncertainty in establishing ADIs

Animal to human extrapolation	Relationship of the NOAEL to the threshold dose
	Prediction of effects at low doses, based on studies conducted at high dose levels
	Relevance to humans – interspecies differences
Interindividual variability in human population	Internal – genetics, gender, disease status
	External – nutrition, drugs, smoking, alcohol, environmental pollutants

the NOAEL in animals and the level of exposure that is deemed to be acceptable for people. Different regulatory authorities use different terms for these safety margins, but the purpose is essentially the same. With respect to food additives, the convention with the SCF and JECFA is to use the term **"safety factor"**, which is intended to provide an adequate margin of safety for the consumer.

$$ADI = \frac{NOAEL}{Safety\ Factor}$$

In recent years there has been a trend toward the use of the term **"uncertainty factor"**, which recognises that the safety factor has to allow for the uncertainties in inter-species extrapolation and adjustments for human variability.

As noted above, JECFA and similar committees have used a default value of 100 for the safety factor for over 40 years. This method of determining the ADI was initially proposed on a pragmatic basis but has been subjected to a number of refinements with experience in use and advances in scientific understanding. Whilst it is a simplistic approach, it actually involves a great deal of expert skill and judgement in determining the nature and relevance of the critical effect, the studies that identify the NOAEL, and whether the database indicates that a safety factor other than the default should be used.

TOXICITY TESTING METHODS

Testing strategies

A number of different types of data are used in establishing the safety of chemical substances for use in foods. These include:

- consideration of the chemical structure and any intended biological activity (e.g. anti-oxidant);
- *in vitro* models, such as cell cultures or tissue slices;
- laboratory animals;
- human volunteers.

Clearly it would not be ethical to give a chemical to human volunteers unless there were a reasonable degree of confidence that they would not be harmed. Ethical considerations also demand that we should minimise the use and suffering of laboratory animals. As a result there is increasing interest in development of alternatives to animals, such as computer modelling and *in vitro* approaches. These models often provide useful mechanistic information, and there are a number of well-established assays for detecting the potential to alter the genetic material. There is progress towards validation of alternative methods for assessing topical effects – such as eye irritation – which are of most relevance to worker safety and safety assessment of cosmetics and toiletries. However, the limitations of most *in vitro* techniques mean that they are not considered suitable for safety assessment of food components, and it is therefore necessary to conduct toxicity testing in laboratory animals. *In vivo* testing should not follow a prescribed format, and testing strategies should be designed specifically, taking into account the nature of the

chemical in question. Many food chemicals have been used for long periods, and previous animal testing, or prior knowledge of safety in use, may influence requirements for future testing. Similarly, a simple checklist of tests should not be followed for the introduction of new food additives. Results of the first tests will influence the development of a testing strategy, possibly indicating non-standard investigations. An extensive battery of tests would be expected for a food additive intended for widespread consumption (see Table 5).

Species selection

As already noted, the aim of toxicity testing in animals is to identify the toxic effects that a chemical produces, which are relevant to humans, and the doses at which these are observed. Ideally, the effects seen in the animal model would be the same as those that might occur in people, but examples of inter-species differences in response to different chemicals are well-recognised. Ideally, a species closely resembling humans, from a kinetic or physiological point of view, should be used, but it is generally not possible to select the animal model that most closely resembles humans early in a testing strategy. In addition, it is desirable to have extensive background information on the pathology and physiology of any experimental animal to allow interpretation of study findings. The convenience of handling and maintenance, as well as the life-span of the animal, must also be considered. As a result, most tests are conducted with small laboratory rodents, particularly the rat, which can be exposed for all stages of life within a reasonable time span (2 years). At a later stage of a testing strategy, studies in a non-rodent species may be required, and additional studies may be performed to establish the relevance of the animal data to humans.

TABLE 5

Main toxicity tests which are appropriate for broad-use food additives

Acute oral toxicity	Single dose study to define extent of toxicity in absence of other data
Short-term toxicity	Repeated daily doses for 14-28 days to provide indication of toxic potential
Subchronic toxicity	Repeated daily doses for 90 days to provide information on major site(s) of toxicity and effects, and to indicate suitable dose levels for chronic studies, usually in two species, rodent and non-rodent
Chronic toxicity and carcinogenicity	Repeated daily doses for 2 years in rodents, providing the data most frequently used in deriving the ADI
Genetic toxicity	Short-term tests for capacity to interact with DNA and to cause mutations or chromosome changes, using a variety of endpoints in bacterial and mammalian systems, *in vitro* and *in vivo*
Reproductive and developmental toxicity	Repeated daily doses before, during and after gestation to determine effects on male and female fertility and on the developing fetus and neonate and possible inheritable effects. Usually involves a multigeneration study in a rodent and developmental toxicity in two species
Immunotoxicity	Investigations on the structure and function of the tissues and cells involved in the immune response (included in short-term and subchronic studies)
Neurotoxicity	Investigations on the structure and function of the nervous system, and on behaviour (included in short-term and subchronic studies)

Study design

A number of guidelines and quality assurance measures have been established in order to ensure that the results of toxicity studies are suitable for use in safety evaluation. Protocols should be designed taking two things into account: the aim to identify doses both with and without effects; and the fact that people may ingest an additive over an entire lifetime. This means long-term animal studies are usually required, but short-term studies are normally conducted first in order to identify early-developing effects and to help in selection of appropriate doses for the longer term studies. Even then, there is no guarantee that the doses will be appropriate. One possibility is that prolonged dosing may lead to tolerance and recovery from early effects, with the result that the long-term study would fail to show any effects. Alternatively, chronic effects may be seen only after prolonged treatment, leading to the possibility that even the lowest dose results in adverse effects and a NOAEL cannot be established. For substances such as food additives, which are of very low toxicity, the highest dose may form a significant proportion of the animal diet, possibly leading to artefactual effects resulting from nutritional imbalance. For this reason, it is generally agreed that the substance should not exceed 5% of the diet or lead to a decrement in bodyweight gain of more than 10% compared with animals receiving the control diet. The numbers of animals per dose group should be sufficient to allow statistical analysis. Adequate control groups must be included in order to ensure that treated animals differ from control animals only with respect to the treatment of interest.

Guidelines for study design are defined by the Organisation for Economic Cooperation and Development (OECD), and other advice has been published by the SCF and JECFA. These guidelines are not strictly defined protocols and allow flexibility in a number of aspects, which should justify the methods selected in terms of the intended use of a chemical. For food chemicals, the compound would normally be given to animals daily in the diet. The observations and measurements that are included in a particular study should be selected taking into account the nature of the chemical under investigation and its likely usage and effects.

Good Laboratory Practice

Toxicity studies should be conducted in compliance with the principles of Good Laboratory Practice (GLP), which is a quality assurance scheme initially introduced to prevent falsification of results. It defines standards relating to management structures, training of personnel and laboratory maintenance within the organisation, as well as the conduct, recording and reporting of all aspects of a study. The principles of GLP are internationally agreed upon and are included in the EU requirements for standard tests. Compliance must be accredited by the appropriate national regulatory body.

Endpoints

The endpoints of a toxicity study are the observations and measurements of potential toxic effects, already summarised in Table 2. A number of observations, such as changes in general appearance and behaviour, and monitoring of food consumption and weight gain, are made frequently throughout the duration of a toxicity study. At the end of a study, and at interim points during a long term study, groups of animals are culled and autopsies performed. At autopsy, visible changes are recorded, and major organs are weighed. Samples of blood and various tissues are taken for biochemical assays and histological observations. Any animals found to be suffering during the course of a study are sacrificed and an autopsy performed in order to attempt to establish the cause.

Toxicity endpoints may be categorised as functional or morphological changes. At the simplest level, a functional change might be a slower rate of weight gain in test animals compared to control animals, which is unrelated to lower food intake. Reduced weight gain is not necessarily associated with detectable pathological effects but may be the only observation seen with relatively innocuous chemicals. Unlike pharmaceutical agents or pesticides, most types of food additive are not designed to have biological activity, and many are of low toxicity; consequently, in order to establish a NOAEL in toxicity studies, it is necessary for them to be tested at high levels.

Morphological changes include phenomena such as liver and caecal enlargement that may be physiological responses to administration of high levels of chemical. In many cases they have little relevance for any kind of effect that may occur in people with more moderate levels of intake. Even when organ damage is observed by microscopy studies, it is necessary to consider whether this has occurred as a direct result of the chemical under investigation, or may have arisen indirectly, for example, due to interference with the animal's nutritional status. Expert committees review all the reported effects in order to establish whether they can be directly attributed to the chemical, whether they are relevant, and whether they may be considered to be "adverse".

Mutagenicity or genotoxicity studies are conducted in order to determine whether a chemical is able to interact with DNA and to cause mutations (heritable changes). The implications of positive results in such studies are a potential to cause congenital abnormalities, if the mutation occurs in the germ cells (ova or sperm cells), or cancer, if the mutation occurs in other cells. These studies are therefore important, both as indicators of potential carcinogenic or reproductive effects, and to provide information on possible mechanisms of effect seen in long term animal studies, particularly for carcinogenicity. Thus, if a chemical has been found to cause an increased incidence of tumours in animals, an expert committee will not automatically conclude that an ADI should not be established but will determine if there is a recognised non-genotoxic mechanism of action, and its relevance to humans. However, it should be stressed that such decisions are rarely straightforward, and results from different studies may produce conflicting evidence that needs to be examined in detail.

Tests for reproductive effects take into account that food additives are consumed by men and women throughout the reproductive stages of their lives, including pregnancy and lactation. A range of studies are conducted in which exposure occurs to the mother during the critical stage of organogenesis, or to both males and females prior to and during mating, and then throughout pregnancy and lactation over a single or multiple generations. Neonatal development may potentially be influenced not only by chemicals (or metabolites) in the mother's milk and in baby foods, but also by influences on maternal behaviour, hormonal balance or nutrition. Particular concern is raised by effects seen in offspring at doses below those which cause maternal toxicity.

More specialised tests (such as for neurotoxicity or immunotoxicity) may be undertaken if results of standard tests, or consideration of the chemical structure, suggest a possible problem. Guidelines for testing methods are continually reviewed, in the light of new scientific understanding, in order to allow incorporation of new approaches that have been shown to be valid and relevant.

Metabolism and toxicokinetic studies

The ways in which studies of absorption, distribution, metabolism and excretion may contribute to safety evaluation of food additives are summarised in Table 6. As noted above, these deal with the way in which the body handles a chemical. The rates of absorption, rates and sites of distribution, and rates and routes of excretion determine the concentration of a chemical and its metabolites to be found at a particular tissue at a particular time after ingestion. The overall biological response therefore results from the balance of a number of different reactions. Comparative information on the balance of these reactions in animals and humans, at low and high doses, and following short-term and long-term exposure, can be used in extrapolation from results of animal studies to humans. In addition, knowledge of the range of variation between individuals will further reduce uncertainty in establishing safe levels for the whole human population. However, in practice the available human data are generally incomplete or absent, and such information is normally used in a qualitative rather than a quantitative manner.

TABLE 6

Role of metabolism and toxicokinetic studies

Identification of relevance of animal species used in toxicity studies	Comparison of pathways of metabolism in animals and humans
	Investigation of toxicity in animals of major metabolites found in humans
	Investigation of role of gut microflora in metabolism
Extrapolation of animal data to humans	Comparison of metabolite profiles after high and low doses
	Comparison of metabolite profiles after short-term and long-term dosing
	Metabolism into normal body constituents
	Mechanistic studies

DERIVATION OF THE ADI

The NOAEL compared with the threshold dose

As already discussed, the toxic effects produced by approved food additives would show a threshold, meaning that the effect only occurs at intakes above that threshold level. Ideally, establishing an ADI should commence with identifying the threshold in a relevant experimental model. In practice, it is not feasible to identify a threshold, for a number of reasons:

- a very large number of animals would be needed in order to detect an effect occurring in a small proportion of them;
- a large number of doses would be needed to be certain of having one close to the threshold;
- the value of an experimentally-determined threshold could be affected by the sensitivity of the available techniques for measuring the adverse effects.

It is therefore normal to use the NOAEL as a surrogate for the threshold. Because toxicity studies are designed to span the dose-response from no-effect to marginal-effect to marked-effect, and because food additives generally have relatively low toxicity, there is frequently a factor of 5 or 10 between doses. For example, if the marginally-effective dose is 10 times the NOAEL, and the threshold is nearer to the marginally-effective dose, then the threshold may be almost 10 times higher than the NOAEL (see Figure 3), again illustrating the conservative approach inherent in deriving the ADI.

Relevance of effects/endpoints

A second uncertainty relates to the relevance of the effects seen in the toxicity studies. Because most food additives are relatively innocuous, it is necessary to test at high levels in the diet in order to obtain an effect. In some circumstances the only effect observed may be reduced weight gain. In the absence of detectable abnormalities, it may not be possible to define changes in body or organ weights as adverse, but they would still be used to derive the ADI.

Some biochemical changes such as the induction of certain enzyme activities may fall into a poorly defined area between a reversible adaptive response and a toxic response. Even if such changes appear to fall within a physiologically normal range, they cannot readily be dismissed as insignificant.

An alternative scenario is that testing at high levels may result in severe chronic effects that are not relevant to lower levels of exposure. This may occur for example if high doses result in the body's detoxication and natural defence mechanisms being overwhelmed, or if a continual cycle of cell damage, repair and regeneration leads to abnormal growth, or even cancer. Interpretation of such aspects are critical for the extrapolation from high dose to low dose.

The pivotal study

The toxicity study (or studies) used to identify the NOAEL for the critical effect may be referred to as the pivotal study (or studies). If studies have been conducted in rat and mouse, with effects seen at lower levels in rats than in mice, then the rat study is considered to be the pivotal study. The exception to this is when sufficient data are available to demonstrate that the most sensitive species is not relevant to humans for the effect in question. This would normally be supported by human data. An example might be if the rat produced a toxic metabolite that was not found in humans.

The quality of the pivotal study is very important in assessing the overall level of uncertainty in establishing a safe human intake. Because animal studies have to be compared to potential lifelong human exposure, a chronic bioassay is normally required. Adverse effects are often seen at lower doses in long-term studies, and so the pivotal study is frequently the chronic bioassay or the multigeneration study. As already noted, the pivotal study should identify the critical effect, if any, and a NOAEL, and should be conducted in compliance with GLP and appropriate study guidelines. The study endpoints should include the most sensitive available methods for detecting the critical effect.

Safety factors

By convention, a default safety (uncertainty) factor of 100 is normally used. Initially, this was an arbitrary decision, but soon became defined as comprising two equal components:

- a factor of 10 for inter-species differences; i.e. to allow for possible greater sensitivity of humans compared with the animal model, due to slower elimination from the body, greater balance of activation to detoxication reactions and/or greater sensitivity to the toxic effect, and
- a factor of 10 to allow for human inter-individual (intra-species) variation, i.e. the possibility that a proportion of the population may be at greater risk because of differences in toxicokinetics or tissue sensitivity within the human population, i.e.

$$ADI = \frac{NOAEL}{10x10}$$

The default 10 x 10 factor is normally used, but there are a number of situations that may lead an expert committee to recommend a different factor.

Inadequate database: The pivotal study may be deemed to be inadequate if it does not meet the criteria defined above. Under these circumstances it may be possible to define a temporary ADI, whilst further studies are conducted. Because of the added uncertainty, a higher safety factor is indicated, such as an additional factor of 2. In the case of unavoidable contaminants, the database may show gross deficiencies and an additional safety factor of 5 or 10 may be applied in establishing the TDI.

Severe irreversible effects: An additional safety factor may be applied when substances have been shown to produce irreversible developmental effects or carcinogenic effects of potential relevance to humans, even by an assumed threshold-based mechanism. For example, the establishment of an ADI for some pesticides, or of a PTWI for contaminants, may involve the use of a higher safety factor (with an extra factor of 5 or 10). In reality, the application of this factor is more related to risk management than to risk assessment, and its use is subject to wide differences between regulatory agencies.

Human data: If data on human toxicity and the dose-response were available, these would be weighted more highly than animal data. The uncertainty in extrapolation would be reduced, and it would not be necessary to allow for possible inter-species differences. A single safety factor of 10 might therefore be considered. However, human toxicity data are usually available from occupational or accidental exposure and not from controlled studies and therefore are often less reliable. Toxicokinetic studies may be conducted in human volunteers because they can be designed to use relatively low levels of a substance that do not have harmful effects. Results of such studies also help in extrapolation, and this is considered further below.

ADI categories

For some additives of low-potential toxicity, evaluation of the available data may lead to the conclusion that the

total potential intake from all possible sources does not represent a hazard to health. In this situation, it may be considered unnecessary to specify a numerical value for the ADI, and the term ***ADI not specified*** is used, as for example with the modified celluloses. However, this does not mean that the additive may be used at any level. The principles of Good Manufacturing Practice should then be applied, i.e. it should be used at the lowest level required to produce the desired technological effect.

Another variation of the ADI has been mentioned above, in relation to the need for a higher safety factor if the database is not adequate. A ***temporary ADI*** may be allocated for a defined period when new questions are raised about an approved food additive, and additional studies are being conducted. It does not imply that consumers are at increased risk, but a larger safety factor (e.g. two-fold higher than otherwise) may be applied as a precautionary measure because of the greater uncertainty. The new data would then be reviewed, resulting either in re-establishment of a full ADI, a request for further work and extending the temporary ADI, or withdrawal of the ADI. In this circumstance it is considered that the relative short exposure to the substance is unlikely to result in harm, but that safety cannot be assured with lifetime exposure.

The ADI normally specifies the maximum acceptable intake for a single chemical substance, but there are a number of situations in which a modified approach is considered appropriate. A ***group ADI*** may be set for compounds that are expected to have additive effects because of similar chemical structure or toxicity. If ten such compounds were all consumed at the level specified by an individual ADI, the combined result would be equivalent to consuming ten times the ADI of just one of them, with the possibility of producing harmful effects. It is therefore considered necessary to control the overall intake of the group. The ADI may be derived from an average of the NOAELs for all of the compounds, but usually, and more conservatively, from the lowest NOAEL of any member. Alternatively the NOAEL may be based on the toxicity of a common metabolite. For example, the assessment of allyl esters is based upon the toxicity of the hydrolysis product, allyl alcohol, and its metabolites.

A recent analysis considered whether there might be a need to take into account possible interactions between different additives that do not share common metabolites or structural similarities. A review of the toxicity data on the additives approved in the EU showed very few examples where interactions were theoretically possible. The few that were identified included substances having similar effects on the liver (curcumin, thiabendazole, propyl gallate and butylated hydroxytoluene), on the kidney (diphenyl, *o*-phenylphenol and ferrocyanide salts) and on the blood (azorubine and propyl gallate). These might be of theoretical concern in exposure situations where the intake of each additive was close to the ADI. However, such situations were not likely to arise, because of low levels of intake, particularly where the additives are alternatives for the same application.

The uncertainties surrounding the value of the NOAEL, and the extrapolation from animals to humans (as summarised in Table 4) mean that the ADI is not a fixed value. Generation of new data could lead to review of the safety evaluation and revision of the ADI. As science develops, new tests may be conducted with more sensitive or relevant endpoints, indicating a lower NOAEL, and in such cases a lower ADI should be considered. Alternatively, additional information may decrease the uncertainties and indicate that a higher ADI could be set. The ADI is not a fixed entity, and the evaluation and review process should have sufficient flexibility to allow new approaches to be incorporated.

NEW DEVELOPMENTS

It has been suggested that derivation of the ADI might be improved in relation to two major points:

1) The use of default safety (uncertainty) factors to allow for inter-species and intra-species differences is viewed as non-scientific;

2) Since it is derived from the NOAEL, which is an imprecise measure of the threshold, it fails to make scientific use of the available information on the dose-response relationship.

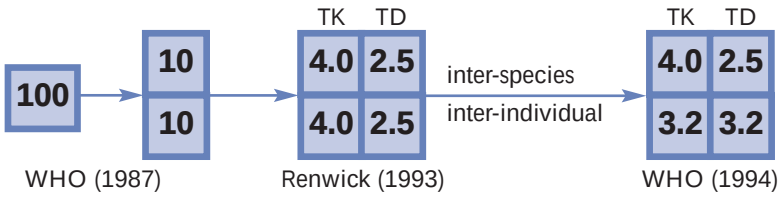
These criticisms have led to attempts to introduce a more scientific approach.

Data-derived safety factors

Use of default safety factors assumes a state of uncertainty, or lack of knowledge, for food additives allocated a numerical ADI value. But there is a great deal of information available on the fate and effects of some specific compounds, and from a scientific viewpoint, it would be preferable for this to be taken into consideration in deriving an ADI.

It is generally agreed that the 100-fold default safety factor comprises two 10-fold factors for inter- and intra-species differences and variability, each attributable to potential differences in the fate and effects of the compound in question. Therefore, logical progression is to consider whether the 10-fold factors could be subdivided into factors for the fate and effect (toxicokinetics and toxicodynamics). Initially, it was considered that toxicokinetic factors were likely to be more important than toxicodynamics, for both inter- and intra-species variability. Subsequent examination of various databases has indicated a differential split, with greater weight given to toxicokinetic causes of inter-species differences, whereas equal weighting may be given to toxicodynamic and toxicokinetic differences in individual variability (Figure 5). If individual data on any of these components were available, they could then be incorporated into the evaluation by replacement of the appropriate default. For example, if information is available indicating that the toxicokinetics of a particular food additive are quantitatively similar in the experimental animal used to establish the NOAEL and in humans, then the default factor of 4.0 in Figure 5 would be replaced by the value of 1. The factors would then be 2.5 for inter-species differences in toxicokinetics and 10 for human variability, giving an overall factor of 25.

FIGURE 5:
Subdivision of the safety factor



(from Renwick and Lazarus, 1998)

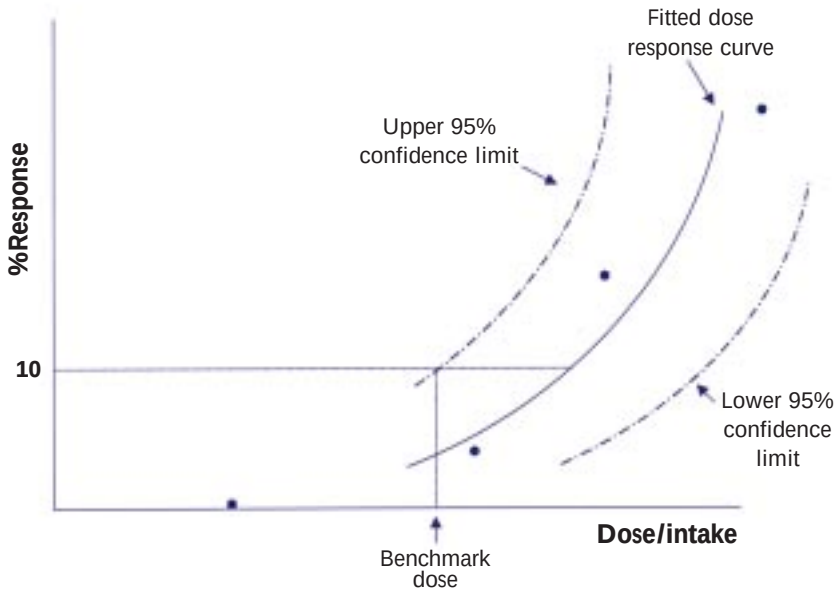
TK – toxicokinetics (fate of the chemical in the body)
TD – toxicodynamics (effects of the chemical on the body)

Analysis of available data indicates that, in general, the default safety factors are appropriate; however, where data on a compound indicate that the defaults are inappropriate (too low or too high), then the subdivision of the factors allows additional data to be used to modify the defaults and introduce compound-specific data.

Benchmark dose

In order to reduce the uncertainty associated with the imprecision of the NOAEL and to make full use of the dose-response curve, proposals have been made for a more precise calculation of a dose that produces a small increase in the level of adverse responses. This dose is referred to as a **"benchmark dose"**, and could be used as an alternative to the NOAEL in order to derive an ADI following the application of safety factors. Like the NOAEL, the benchmark dose is a surrogate for the threshold dose, but it is less dependent on the dose selection and is expected to be more closely related to the threshold than is the NOAEL. Figure 6 shows a typical example of how a benchmark dose can be calculated. A mathematical model is applied to the experimental data in order to produce a dose-response curve of best fit within the individual datum points. The statistical calculation assigns limits to either side of the curve, within which there is 95% confidence that the dose-response curve should occur. Use of the 95% confidence interval has the advantage of taking into account the quality of the data, because a weak study with few animals per dose group, or a poor dose-response relationship would produce wider confidence limits than a good study. The upper confidence limit is used as a conservative approach to allow for the uncertainty in the experimental data. From the fitted dose-response, the dose that coincides with the upper confidence limit for the 10% response is defined as the benchmark dose (5% response could also be used).

FIGURE 6
The Benchmark dose



Another advantage of the benchmark approach is that it can be applied to studies that have failed to identify a no-effect level. However, it is not applicable for all types of toxicity and is not of value when adverse effects are not observed, when effects occur only at the top dose, or at low frequency, i.e. in situations often encountered with food additives.

INTAKE CONSIDERATIONS

A food additive is considered safe for its intended use if the total human intake is less than or similar to the ADI. The intake estimate should include any natural sources of the additive as well as sources from deliberate addition to food. An accurate estimate of total human intake requires information on all the types of food in which an additive is contained, the levels of additive within those foods, and the amount of those foods that are consumed. Clearly there are enormous differences in dietary habits between individuals, and even for a single individual consumption of specific food items will vary from day to day, and with different seasons and periods in life. Comparison of intakes with the ADI usually adopts a tiered system, starting with a simple screen to prioritise substances for which new information is required, leading to sequential increases in complexity and accuracy of approach if considered necessary.

Intake estimation

The simplest type of approach uses indirect measures of intake averaged across a whole population, which is sometimes referred to as the *per capita* approach. For example, a very approximate estimate of intake can be obtained by determining the annual amount of an additive produced and imported into a country (less the amount exported) and dividing that value by the population figure. Because more refined estimates (see below) usually consider intakes by "consumers only", the *per capita* figure can be corrected by assuming that only a proportion (e.g. 10%) of the population are consumers. Another *per capita* approach is to estimate the overall amount of foods consumed per year multiplied by the concentration of the additive that is normally used and the proportion of foodstuffs in which it is contained. These data can be related to body weight for comparison with the ADI.

These indirect methods are inexpensive but they do not provide information on individual intakes. Failure to include an estimation of the proportion of the population who do not consume a particular food means that the average will be an underestimate of the intake for many who do consume it. Similarly, averaging food consumption over a year will give an average daily intake that underestimates the actual intake in a single day for a food that is consumed infrequently.

Thus intake estimates provide an average for a population, but no indication of the range of intakes within that population. The *per capita* average cannot be used directly to establish whether intake is in compliance with the ADI. However, if the *per capita* average indicates that intakes are approaching the ADI, then it would raise concern that those individuals with higher than average intake could be exceeding the ADI. As an empirical guideline, it is assumed that the 5% of a population with the highest intake will consume 3 times as much as the average consumer (this is referred to as the 95th percentile intake level). Conversely, if the *per capita* average is very much lower than the ADI, then there is less cause for concern. In this way, data from intake estimations can be used in prioritisation of food additives for more accurate study.

The **budget method** was developed by Hansen of the National Food Administration of Denmark to establish maximum-use levels of additives in food and beverages, based on theoretical food and drink intakes derived from extreme physiological requirements for energy and liquid. It is extremely conservative because it assumes that one-half of all foods contributing to the energy intake, and all beverages contributing to the liquid intake, contain the additive. A similar approach has been used to determine if the maximum permitted-use levels could theoretically give an intake greater than the ADI; this estimate is termed the Theoretical Maximum Daily Intake (**TMDI**). Studies have shown that the budget method grossly overestimates actual intake, and it is therefore viewed as a "most conservative" or "most cautious" approach, which is appropriate for a preliminary screen. If the TMDI is lower that the ADI then it is difficult to envisage any real-life situation in which the ADI would be exceeded. If the TMDI is higher than the ADI, then more detailed studies are required, and these are based on consumption data for groups of relevant, defined processed foods (rather than all foods).

Food consumption data

In order to have more accurate estimates of additive intake in subgroups of the population, it is necessary to have data on consumption of different food types.

Recall methods involve reports of the type and quantities of food and drink that were consumed by individuals over a specific period, usually the previous 24 hours.

Food frequency questionnaires (**FFQs**) request information on how often an individual consumes various types of food. They are generally limited to less than 100 food types but can be designed to focus on specific issues.

Both recall methods and FFQs may include estimates of the quantities consumed but cannot provide accurate quantitative data. However, they are useful for indicating the proportion of a population that consumes a particular foodstuff.

A **diet diary**, in which subjects record everything they eat over a fixed period of time, provides more quantitative information from food consumption studies. This is the most sophisticated method of

TABLE 7

Influence of survey duration on % consumers and average intake of consumers for a hypothetical food additive

Subject	Day 1 (mg/day)	Day 2 (mg/day)	Day 3 (mg/day)	Day 4 (mg/day)	Days 1-4 (mg/day)
1	100	100	100	100	100
2	0	100	0	0	25
3	100	0	0	100	50
4	0	100	0	100	50
5	0	0	0	0	0
% consumers	40%	60%	20%	60%	80%
Population average intake	40 mg/day	60 mg/day	20 mg/day	60 mg/day	45 mg/day
Consumers only average intake	100 mg/day	100 mg/day	100 mg/day	100 mg/day	56 mg/day

obtaining intake information, as it can identify particular brands of product, and incorporate the actual level of additive contained in them, rather than assuming a maximum usage level. Portions of food may be weighed and the intake of additive identified from the known concentration, or duplicate portions are prepared so that one can be analysed for actual content.

Ideally, the consumption patterns would be monitored over prolonged periods because the ADI relates to the whole lifetime. However, practicality dictates that detailed studies are conducted over periods of a few days, and so it is necessary to understand and make allowances for the limitations of the methods used. The results of food consumption surveys are highly dependent upon the duration of the study. Staple foodstuffs such as bread and milk may have a relatively constant pattern of consumption, whereas other foods may be consumed infrequently or seasonally, and with an intake ranging from zero to high levels. As the length of study increases, an increasing number of the participants are likely to consume an item that is consumed infrequently. This has two implications. First, the longer the study, the higher the proportion of participants who will be defined as consumers of a given food type. Second, if consumers do not consume that food every day, their average daily intake over the study period will be reduced. This is illustrated in Table 7. Thus food surveys of longer duration provide more reliable estimates of usual food intake and are able to identify the range of intakes within groups of individuals. However, they are expensive and time-consuming to conduct. Also participants are more likely to withdraw from longer studies due to the inconvenience, and the reliability of completion of the food diary decreases after a few days.

A combination of a FFQ with a 3-day diet record has been proposed as a compromise solution. The 3-day diet record indicates the total population intake and the FFQ

can be used to estimate the proportion of the population that consumes a specific food type over a longer period. Combining these two sets of data gives the average intake for consumers but may not be sufficiently accurate to define the highest intake levels.

Because their distribution within the food supply is not controlled as happens for additives, the validity of intake estimates for contaminants can be checked by conducting duplicate portion (or total-diet) surveys. Foods are selected as representative of a normal diet for the population and levels of the chemical in the food mixtures or individual foodstuffs are measured using sensitive analytical techniques. This provides the most realistic data because it does not assume that the substance is always present at the maximum permitted level. Potentially, the duplicate portion method could be used to study possible "high-risk" groups thought to be at higher risk than average, either because of extremes in dietary habits which could result in higher levels of intake, or because of greater susceptibility. However, in practice it involves high levels of expertise and equipment that do not make it feasible for routine use.

The more sophisticated methods of estimating intake of additives and pesticides may allow mathematical analysis of the range of intakes amongst consumers. It is then normal to compare the ADI with a level of intake that is in the upper range of the distribution. It is worth noting that different entities use different percentiles to represent high consumers, and this may lead to differences in interpretation of results. For example, whereas the EU uses the 95th percentile (i.e. 95% of the population consume at this level or less), it is local policy within the UK to use the 97.5th percentile and in the USA to use the 90th percentile.

Limitations of intake data

The *per capita* and budget methods of estimating intake are crude, worst-case approaches that can be valuable as inexpensive screens but are gross over-estimates of daily intakes. Food consumption data, whether generated by recall methods or diet diaries, are more realistic but are still subject to a number of uncertainties and imprecision, as summarised in Table 8. There is no ideal method of obtaining intake data, because the results obtained are influenced by the period over which intake is assessed. Surveys are more relevant to normal patterns of consumption if conducted over a longer period, but subjects are more likely to produce accurate diaries over a shorter period. Any survey is therefore a compromise between these two factors. In addition, individuals tend to misreport consumption of some food types, for example over-reporting of foods that are perceived as good (healthy) and under-reporting of foods perceived as bad (unhealthy, self-indulgent, etc.).

The dietary habits of a single individual will vary enormously from day-to-day, at different times of the year, and over the entire lifetime. Technological uses of individual additives may also change if considered over prolonged periods of time. It is simply not plausible to estimate human intake of a food additive in any way that is comparable to the defined dose administered in animal studies. Therefore the aim is to identify potential maximum daily intakes as worst-case scenarios, recognising that all available methods are imprecise. In most cases, very few individuals (if any) will actually have the maximum daily intake, and they will not have that maximum daily intake every day throughout their entire lives.

TABLE 8

Limitations in establishing intakes of food additives and contaminants

Per capita estimates	Estimated average consumption for entire population • assumes all individuals are "consumers" • assumes all of the additive produced/imported is consumed > gives no indication of range of intake
Budget estimates	Estimated maximum intake • assumes all foods for which it is permitted contain the additive at maximum approved level > grossly overestimates intakes
Use-related estimates	Estimated maximum intake from defined foods • assumes foods contain additive at maximum approved level • requires information on consumption
Recall methods	Report of foods and drink consumed over previous 24 hours • short-term report may not be representative of longer-term dietary habits • inaccurate estimates of amounts consumed • may assume maximum-use levels or measure actual contents in foods and beverages • mis-reporting
Diet diary	Records of all food and drink as it is consumed • quantities usually standardised (e.g. small, medium, large) • results dependent on time period of study • short-term report may not be representative of longer-term dietary habits • may assume maximum-use levels or measure actual contents in foods and beverages • mis-reporting
Duplicate portions	Duplicate portions of all food and drink as it is consumed • expensive and therefore only feasible for short periods of study • short-term report may not be representative of longer-term dietary habits • normally measures actual contents in foods and beverages • mostly used for contaminants of concern • mis-reporting

APPLICABILITY OF THE ADI TO SUBGROUPS

Infants and children

The ADI is defined as an amount of chemical that can be ingested daily over a lifetime without appreciable health risk. However, there has been ongoing debate on the question of whether it affords protection to all sectors of the human population. Focus has particularly centred on the issue of whether infants (from birth to 12 months of age) and children (1 to 12 years of age) are adequately protected by the ADI, because of the hypothetical concerns that:

a) infants and children may differ in their capacity to detoxify and eliminate chemicals from the body (toxicokinetics);

b) infants and children may be more sensitive to toxicity (toxicodynamics).

In addition, different dietary requirements and habits may result in intakes of some additives exceeding the ADI.

Infants below the age of 12 weeks are viewed as a special case. Despite the fact that derivation of the ADI allows for possible effects on neonatal animals, it is not considered appropriate to apply this to the youngest age group. There are two reasons for this:

1. Very few data are available with respect to the effects of chemicals on very young infants. It is known that the levels of enzymes responsible for biotransformation are generally very much lower in the newborn, particularly in the pre-term infant. Lower levels of enzyme activity can potentially lead either to impaired detoxication or to decreased formation of toxic metabolites. There are also some types of toxic effect to which the neonate is more sensitive, as a result of its rapidly changing physiology. These factors increase the uncertainty in establishing safe levels of intake for the infant in the first few weeks of life.

2. Exposure to suckling animals via the mother's milk mimics the situation of the breast-fed infant, but routine studies do not simulate direct exposure to additives in infant milk formula.

Therefore, in principle, food additives are not permitted in infant formulae. In exceptional circumstances in which an additive is essential for technological purposes, then particular concern is paid to the potential for adverse effects in neonatal animals during toxicity studies.

The available scientific data do not support suggestions that older infants and children would be at greater risk from food additives than adults. As already noted, there are a large number of biochemical and physiological changes occurring in the early stages of life. These may influence the rates of absorption, distribution, metabolism and excretion from the body. In particular, the various enzymes involved in metabolism of ingested chemicals develop rapidly, but at different individual rates, in the first few weeks after birth. Similar changes occur in the neonatal rodent, although not necessarily at the same stages of development. However, although individual enzymes and physiological functions may show large differences between infants and adults, these differences do not seem to have major implications for the fate of chemicals taken into the body. Studies of elimination of a wide range of drugs have shown that the rate of elimination from the infant body was similar to, or in some cases higher than that for the adult. This means that variation between infants and adults is easily encompassed within the "toxicokinetic safety factor". It also raises the possibility that this part of the

safety factor is larger than needed for infants and children, which leaves a larger component of the default safety factor to allow for possible heightened tissue sensitivity.

There are examples (e.g. lead, nitrate) for which the newborn animal or human has been found to be more sensitive to toxicity than adults. Conversely, the infant is less sensitive in some instances (e.g. to kidney toxicity from aminoglycoside antibiotics), and no general assumptions can be made. The reproductive studies described above are designed to cover all stages of conception, gestation and development and have the potential to detect effects on the fetus, the newborn and the immature animal as well as on the adult. If effects are seen in the developing offspring, then these studies should be influential in establishing the ADI. Thus the design of the toxicity studies allows for the potential (although infrequent) situation in which infants may be more susceptible than adults. There are some concerns as to whether the currently available testing methods are sufficiently able to detect functional changes in the developing nervous, reproductive, endocrine and immune systems, particularly where such changes occur in the adult as a delayed result of effects on the developing fetus or immature animal. This is more likely to be an issue with contaminants and pesticide residues than with food additives which tend to be relatively innocuous.

Overall, the scientific evidence suggests that infants and children are protected by the ADI.

The possibility that infants and children may be more likely to exceed the ADI for a particular substance is based upon two factors. First, the nutritional requirements (e.g. for energy, protein, water) of infants and young children is 2-5 times higher than for adults, when expressed in relation to body weight. Second, they are likely to have a less varied diet, with the gradual introduction of solid foods and subsequent childhood preferences for particular types of food. As a result, young children consume up to 5 times more dairy products, puddings and confectionery than adults – again expressed in relation to bodyweight. The difference in consumption of soft drinks and fruit juice is even larger. Clearly this means that children may consume more of the additives that are included in these preferred foods, than does an adult with a more varied diet. Such considerations do not influence the derivation of the ADI but should be taken into account on a case-by-case basis during the risk management stage of setting limits for the use of additives in specific foods and beverages, in order to ensure that the ADI is not exceeded.

Other susceptible groups

In addition, there are some genetic polymorphisms and clinical conditions that predispose individuals to certain forms of toxicity. For example, people with the genetic disease phenylketonuria have an enzyme deficiency resulting in the inability to metabolise the amino acid, phenylalanine, and are therefore at risk of suffering brain damage due to high blood levels of this amino acid. They are advised not to consume foods containing the artificial sweetener aspartame because phenylalanine is one of aspartame's components. It should be noted however, that phenylalanine is an essential amino acid that is mostly obtained from protein. People with phenylketonuria are at much greater risk from phenylalanine contained in food protein than from aspartame and have to follow a strictly controlled diet with special proteins and pure amino acids.

A special and important case is that of food allergy. Once an individual is sensitised to a particular substance, there is no safe level of intake; even a trace of the substance may be sufficient to provoke a severe, and potentially

life-threatening response. Food allergies most commonly involve the proteins found naturally in certain types of food (e.g. peanuts, eggs, cow's milk), and there are very few convincing reports of allergy to food additives. Where effects have been reported, it mostly appears that the additives exacerbate a pre-existing condition rather than induce a new condition. An example is sulphites, used as preservatives, which may provoke an asthma attack in some asthmatic individuals. Many of the reported cases of food intolerance are anecdotal and subsequent clinical challenge studies often do not support a diagnosis of allergy.

People with true food allergies cannot be protected by the ADI, and must learn to "manage the risk" by avoiding foods containing the substance to which they are allergic. An ILSI Europe Concise Monograph is available on "Food Allergy and Other Adverse Reactions to Food". Accurate food labelling is obviously essential for susceptible individuals to avoid the food-borne allergens from which they are at risk.

SIGNIFICANCE OF EXCURSIONS OF INTAKE ABOVE THE ADI

Just as the NOAEL is not equivalent to the threshold for toxicity in the experimental animal, the ADI is not a threshold for harmful effects in humans. It is intended to indicate a level of daily intake that is considered safe over a lifetime's exposure and gives no indication of what should be considered an "unsafe" intake.

In addition to the obvious safety factor, the overall approach to the ADI includes a number of precautionary measures, which will provide a hidden and undefined margin of safety. Hidden safety margins may be introduced by the following:

- the NOAEL is normally lower than the threshold for toxicity because of the wide spacing between dose levels;
- the assumption that humans are 10-fold more sensitive than the most sensitive animal species is a "worst case" scenario;
- multiplication of the inter- and intra-species factors is another worst case scenario since there is no indication that these are linked;
- the commonly performed methods of intake estimation are over-estimations;
- changing dietary patterns mean that even an individual with extreme dietary habits is unlikely to have high intakes daily over an entire lifetime.

There are two basic scenarios which have the potential to result in intakes of chemical substance in excess of the ADI or TDI:

1. Some individuals may regularly consume very high amounts of a particular food type resulting in greater than expected intakes of the additives. An example of this might be diabetics consuming carbonated drinks containing artificial sweeteners, with additional use of table-top sweeteners. This pattern of consumption may persist over relatively long periods. When recognised, such groups are usually a focus for attention in intake surveys.
2. A batch of a particular foodstuff may contain more than the permitted level of a chemical. This is most likely to occur when an isolated incident results in contamination of the food with, for example, a pesticide.

Taking into account both the hidden and overt safety margins, the JECFA concluded that occasional excursions above the ADI will not result in harm, provided that intakes averaged over a longer period are below the ADI. Excursions above the ADI are generally undesirable, particularly for prolonged periods. However, it is not possible to define in general a frequency or degree of excursion that would be harmful. The likelihood of harm occurring will depend upon the duration and magnitude of the excess intake in comparison with the specific toxicological data, the toxicokinetics of the compound, and the duration of the pivotal study used in derivation of the ADI. If the ADI is exceeded for a relatively short period, it may be possible to compare the intake with the NOAEL from a toxicity study of shorter duration, in order to establish whether the safety margin is adequate. A number of mathematical modelling approaches are being developed for estimation of both exposure and risk, which might help the risk manager to quantify risks and to make an informed decision on the action to be taken following the identification of excessive intake.

SUMMARY AND CONCLUSIONS

The Acceptable Daily Intake, commonly known as the ADI, is an estimate of the amount of a food additive that can be ingested daily over a lifetime without appreciable health risk. It has been in use for about 40 years and is applied to pesticide and veterinary drug residues in food as well as to food additives. It is established by expert scientific committees, following evaluation of all available data relating to the effects of the substance in studies conducted in humans, in experimental animals and with *in vitro* systems. From all of these studies, a judgement is made concerning the adverse effect that is of most relevance to humans, and the highest dose at which that effect does not occur under experimental conditions – referred to as the No Observed Adverse Effect Level (NOAEL). The NOAEL is divided by a safety factor to allow for the uncertainties involved in the extrapolation of the results obtained under experimental conditions to a level of intake that is considered safe for the entire human population (with the possible exceptions of infants under the age of 12 weeks and individuals who are allergic to the additive in question). The level of intake obtained by this calculation is the ADI.

The safety factor was initially proposed on an arbitrary basis, but recent studies based on developments in scientific knowledge have shown that the default values are justifiable and may be modified to allow incorporation of more data as they become available.

A number of different methods are available for estimating intake of food chemicals, whether for the whole population of a given country, or for specific subgroups of the population. Initial methods of intake estimation provide overestimates of realistic intakes. Comparison of the overestimated intakes with ADIs, combined with the safety margins within the ADI, ensures that the consumer is well-protected against any potential harmful effects of chemical substances in food. More complex and accurate methods may be used if the simple methods indicate that intake could be close to the ADI, or in situations of specific concern.

Because the ADI is usually based on the NOAEL from lifetime feeding studies, occasionally exceeding the ADI is not a health concern. However, the significance of longer-term intakes above the ADI need to be considered on a case-by-case basis. If it appears that the ADI may be exceeded in some circumstances, then appropriate risk management procedures would be instigated in order to reduce the intake.

Toxicity testing and intake-estimation methods are undergoing a continuing process of evolution and refinement. The methodology used in establishing the ADI is sufficiently flexible to allow for new technological developments and incorporation of new approaches that reduce the uncertainties involved in safety evaluation. In this way the ADI will continue to be of value well into the 21st century.

GLOSSARY

Acceptable Daily Intake (ADI): Estimate of the amount of a substance in food or drinking water, expressed on a body mass basis (usually mg/kg body weight), which can be ingested daily over a lifetime by humans without appreciable health risk.

Acute toxicity: Adverse effects occurring within a short time (usually up to 14 days) after administration of a single dose of test substance, or after multiple doses administered within 24 hours.

ADI not specified: A term applicable to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food does not [in the opinion of JECFA] represent a hazard to human health.

Adverse effect: Change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences.

Carcinogen: Agent (chemical, physical or biological) which is capable of increasing the incidence of malignant neoplasms (commonly referred to as cancer).

Chronic toxicity: Adverse effects following continued exposures over an extended period of time.

Detoxication: Process(es) of chemical modification which are usually catalysed by enzymes and which reduce or abolish the toxicity of a chemical.

Effect: A biological change in an organism, organ or tissue.

Exposure: Concentration or amount of a particular chemical agent that reaches the target population, organism, organ, tissues or cell, usually expressed in numerical terms of substance concentration, duration and frequency.

Genotoxicity: Ability to cause damage to genetic material. Such damage may be mutagenic and/or carcinogenic.

Group ADI: An ADI established for a group of compounds that display similar toxic effects, thus limiting their cumulative intake.

Hazard: Set of inherent properties of a substance, mixture of substances or a process involving substances that, under production, usage or disposal conditions, make it capable of causing adverse effects to organism or the environment, depending on the degree of exposure.

***in vitro*:** Literally “in glass”, referring to a study in the laboratory usually involving isolated organ, tissue, cell or biochemical systems.

***in vivo*:** In the living body, referring to a study performed on a living organism.

Long-term toxicity study: A study in which animals are observed during the whole life span (or the major part of the life span) and in which exposure to the test material takes place over the whole observation time or a substantial part thereof. The term chronic toxicity study is used sometimes as a synonym for "long-term toxicity study".

Maximum Residue Limit (MRL) for pesticide residues: Maximum contents of a pesticide residue recommended [by Codex] to be legally permitted in or on food commodities and animal feeds. MRLs are based on data obtained following good agricultural practice.

Maximum Residue Limit (MRL) for veterinary drugs: Maximum contents of a drug residue recommended [by Codex] to be legally permitted in or on food commodities and animal feeds. The MRL is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the ADI.

No ADI allocated: Terminology used in situations where an ADI is not established for a substance under consideration because (a) insufficient safety information is available; (b) no information is available on its food use; (c) specifications for identity and purity have not been developed; or (d) the substance is considered unsafe for use in food.

No observed effect level (NOEL): The greatest concentration or amount of an agent, found by study or observation, that causes no detectable alteration of morphology, functional capacity, growth, development or lifespan of the target.

No observed adverse effect level (NOAEL): The greatest concentration or amount of an agent, found by study or observation, that causes no detectable adverse alteration of morphology, functional capacity, growth, development or lifespan of the target.

Provisional Maximum Tolerable Daily Intake (PMTDI): The end-point used by the JECFA for contaminants with no cumulative properties. Its value represents permissible human exposure as a result of the natural occurrence of the substance in food and in drinking water. In the case of trace elements that are both essential nutrients and unavoidable constituents of food, a range is expressed, the lower value representing the level of essentiality and the upper value, the PMTDI.

Provisional Tolerable Weekly Intake (PTWI): The end-point used by the JECFA for food contaminants such as heavy metals with cumulative properties. Its value represents permissible human weekly exposure to those contaminants unavoidably associated with the consumption of otherwise wholesome and nutritious food.

Risk assessment: A scientific, ideally quantitative, assessment of potential effects at given exposure levels.

Safety factor: A factor applied to the no-observed-adverse-effect-level to derive an ADI. The value of the safety factor depends on the size and type of population to be protected and the quality of the toxicological information available.

Short-term toxicity study: An animal study (sometimes called a subacute or subchronic study) in which the effects produced by the test material, when administered in repeated doses (or continuously in food or drinking water) over a period of about 90 days, are studied.

Temporary ADI: Used when data are sufficient to conclude that use of the substance is safe over the relatively short period of time required to generate and evaluate further safety data, but are insufficient to conclude that use of the substance is safe over a lifetime. A higher-than-normal safety factor is used when establishing a temporary ADI and an expiration date is established by which time appropriate data to resolve the safety issue should be submitted.

Tolerable Daily Intake (TDI): Regulatory value equivalent to the Acceptable Daily Intake, used for food contaminants. It may be expressed in mg/person, assuming a body weight of 60 kg.

Uncertainty factor: An alternative description of safety factor, which is being used increasingly because it indicates that the factor is to allow for uncertainties in the risk assessment process.

Acronyms and abbreviations used in this monograph

ADI	Acceptable daily intake
CCFAC	Codex Committee on Food Additives and Contaminants
ECE	Economic Commission for Europe
EPA	US Environmental Protection Agency
FAO	Food and Agriculture Organisation of the United Nations
FDA	US Food and Drug Administration
FFQ	Food frequency questionnaire
GLP	Good Laboratory Practice
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	Lowest observed adverse effect level
MRL	Maximum residue level
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OECD	Organisation for Economic Co-operation and Development
PMTDI	Provisional maximal tolerable daily intake
PTWI	Provisional tolerable weekly intake
RfD	Reference dose
SCF	Scientific Committee on Food (formerly the Scientific Committee for Food)
TDI	Tolerable daily intake
TMDI	Theoretical maximum daily intake
WHO	World Health Organisation
WTO	World Trade Organisation

FURTHER READING

More details of the principles and methodology described in this monograph may be found in:

Barlow, S., Pascal, G., Larson, J.C. and Richold, M. (eds) (1999). ILSI Europe Workshop on the Significance of Excursions of Intake above the Acceptable Daily Intake (ADI). *Regulatory Toxicology and Pharmacology*, **30**, 2/2, S1-S12.

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