When determining ADIs, the 100-fold safety factor is used as the starting point for extrapolating animal data to man and may be modified in the light of the data that are available and the various concerns that arise when considering these data. Some of these are given below:

1. When relevant human data are available, the 10-fold factor for inter-species variability may not be necessary. However, relatively few parameters are studied in man in the assessment of pesticide safety, and data on oncogenicity, reproduction, and chronic effects are rarely available. Thus, even if the parameter measured in humans is the same as the most sensitive adverse effects measured in the experimental animal (e.g., erythrocyte cholinesterase depression), uncertainty still remains with respect to the potential effects on other parameters. This usually necessitates an increased safety factor. Consequently, JMPR rarely utilizes safety factors as low as 10-fold.

2. The quality of the data supporting the NOAELs determined in the animal experiments (and also in human experiments) influences the choice of the safety factor. Unfortunately, toxicity studies are rarely perfect in all respects. While a study may serve to answer a basic question, the degree of certainty with which the question is answered may be reduced by, for example, increased mortality in all groups in an oncogenicity study, resulting in marginally-acceptable data being available at the termination of the study. When a request for a repeat study is not fully justified, an increased safety factor may be utilized under such circumstances.

3. The quality of the total data base may affect the choice of safety factor. Significant data deficits may warrant an increased safety factor due to increased uncertainty.

4. The type and significance of the initial toxic response may alter the safety factor. Thus a response which is reversible may result in a reduced safety factor.

5. The limited numbers of animals used in oncogenicity studies limits the sensitivity of the study in the identification of a threshold dose. When evidence of neoplasia has been identified, safety factors may be increased depending on the available ancillary data and the establishment of an NOAEL.

6. The shape of the dose/response curve (in those cases where data are adequate to permit derivation of such a curve) may also be considered in assessing safety factors.

7. Metabolic considerations may influence the choice of the safety factor. Thus, saturation of

metabolic pathways resulting in toxic manifestations, biphasic metabolic patterns, and data on comparative metabolism may all affect the magnitude of the safety factor.

8. Knowledge of the comparative mechanism of toxic action in experimental animals and man may influence the choice of safety factor.

Several of the factors cited above may apply in the consideration of any one compound. Certain factors may serve to increase and others to decrease the choice of the final safety factor. Therefore, it must be stressed that the total weight of evidence has to be considered in determining the appropriate safety factor to be used and that the determination of safety factors must be considered on a case-by-case basis.

9.3 Allocating the ADI

9.3. 1 Background

The FAO/WHO Joint Meeting on Principles Governing Consumer Safety in Relation to Pesticide Residues indicated that the assessment of the amount of pesticide to which man can be exposed daily for a lifetime, without injury, was the primary aim of toxicological investigations. The Meeting indicated that "when the (toxicological) investigations are completed, it is possible, by the use of scientific judgement, to name the acceptable daily intake." [32, p. 9]. The meeting also defined the ADI as follows:

"The daily dosage of a chemical which, during an entire lifetime, appears to be without appreciable risk on the basis of all the facts known at the time. 'Without appreciable risk' is taken to mean the practical certainty that injury will not result even after a lifetime of exposure. The acceptable daily intake is expressed in milligrams of the chemical, as it appears in the food, per kilogram of body weight (mg/kg)." [32, p. 5].

The first JMPR adopted this definition and discussed the concept of the ADI. The Meeting stated that the following information should be available in order to arrive at an ADI:

(a) "the chemical nature of the residue. Pesticides may undergo chemical changes and are frequently metabolized by the tissues of plants and animals which have been treated with them. Even when a single chemical has been applied, the residues may consist of a number of derivatives with

distinct properties, the exact nature of which may differ in animals and plants and in different crops and products.

(b) the toxicities of the chemicals forming the residues from acute, short-term and long-term studies in animals. In addition, knowledge is required of the metabolism, mechanism of action and possible carcinogenicity of residue chemicals where consumed.

(c) A sufficient knowledge of the effects of these chemicals in man." [35, p. 6].

The Meeting also noted that the identity of the food bearing the chemical should theoretically be immaterial; that the ADI was an expression of opinion, which carried no guarantee of "absolute" safety; that new knowledge or data could always lead to re-evaluation of an ADI; and that JMPR would confine itself to proposing a single set of ADI figures for pesticides. Finally, the Meeting stated that "The proposed levels (of ADIs) could normally be regarded as acceptable throughout life; they are not set with such precision that they cannot be exceeded for short periods of time." [35, p. 7] (see section 9.3.3).

Although the ADI can be exceeded for short periods of time, it is not possible to make generalization on the duration of the time frame which may cause concern. The induction of detrimental effects will depend upon factors which vary from pesticide to pesticide. The biological half-life of the pesticide, the nature of the toxicity, and the amount by which the exposure exceeds the ADI are all crucial.

The large safety factors generally involved in establishing an ADI also serve to provide assurance that exposure exceeding the ADI for short time periods is unlikely to result in any deleterious effects upon health. However, consideration should be given to the potentially acute toxic effects that are not normally considered in the assessment of an ADI.

The principles discussed above were adopted by subsequent Joint Meetings but, as would be expected, have been further developed with time. Thus the 1968 JMPR [42] indicated that metabolites would, under certain conditions, be considered to be included in the ADI. Generally, if the metabolites in food commodities are qualitatively and quantitatively the same as those observed in laboratory test species, the ADI would apply to the parent compound as well as to metabolites. If the metabolites are not identical or not present at the same order of magnitude, separate studies on the metabolites may be necessary. When one or several pesticides are degradation products of another pesticide, a single ADI may be appropriate for the pesticide and its metabolites, e.g., oxydemeton-methyl, demeton-*S*-methyl sulfone and demeton-*S*-methyl [183].

In 1973, when considering the accuracy with which ADIs or TADIs could be estimated, JMPR

recommended that ADIs Should be expressed numerically using only one significant figure [52]. The use of more than one significant figure might be taken to imply a greater degree of accuracy than that which can be achieved when assessing the hazard from the wide range of factors that influence toxicity.

9.3.2 Temporary ADIs

Use of the TADI, first proposed by the Scientific Group on Procedures for Investigating Intentional & Unintentional Food Additives [169], was adopted by JMPR in 1966. Criteria were set that had to be met prior to the establishment of the TADI. These included the consideration of each chemical on its own merits, the establishment of the TADI for a fixed period (usually 3-5 years), and the subsequent review of original and new data prior to the expiration of the provisional period.

The establishment of a TADI has always been accompanied by a requirement for further work by a specified date and by the application of an increased safety factor. The 1972 JMPR considered the course of action to be taken if requested data were not forthcoming and indicated that, under these circumstances, the TADI would be withdrawn. It emphasized, however, that such an action "did not necessarily indicate a potential health hazard, but only that insufficient information is available at the time of review to permit the Meeting to state with reasonable certainty that there is no likelihood of adverse effects on health resulting from ingestion over a prolonged period." [50, p. 7].

In 1986 [76], JMPR indicated that the previously utilized terms "Further work or information required" or "Further work or information desirable" were being replaced, the former by the statement "Studies without which the determination of an ADI is impracticable", and the latter by the statement "Studies which will provide information valuable to the continued evaluation of the compound." These new statement not only reflect the actual work performed by JMPR much more clearly than the previous terms "Required" and "Desirable", but they also reflect the Meeting's increasing reluctance to allocate temporary ADIS as well as the desire to continue the evaluation of a compound even after an ADI has been allocated.

In 1988 [79], JMPR recommended that TADIs should not be allocated for new compounds and that an ADI should not be allocated in the absence of an adequate data base. The Meeting intended that monographs be published for all chemicals which are reviewed, regardless of whether an ADI is allocated, and that data requirements will be clearly specified for those chemicals with an inadequate data base.

The concept of the "conditional acceptable daily intake", adopted by the 1969 JMPR [44], was limited to those compounds for which the use was at that time considered essential but for which the toxicological ,data base was incomplete. This concept, which is unacceptable, has been abandoned.

9.3.3 Present position

The minimum data base normally utilized in determining an ADI comprises short-term feeding studies, long-term feeding studies, carcinogenicity studies, multigeneration reproduction studies, teratogenicity studies, and acute and repeated exposure metabolic, toxicokinetic, and toxicodynamic data. Where deemed necessary, additional special studies may also be required, e.g., genotoxicity studies.

The NOAEL from the most appropriate study divided by the appropriate safety factor determines the ADI. The lowest NOAEL is not necessarily the basis for the ADI (see section 8.2.1). Thus, even though the NOAEL from a chronic toxicity study may be less than that from a reproduction study, the latter may serve as the basis for assessing the ADI, because of the potential use of a higher safety factor (see section 9.2). On this basis, the entire age range of the population is normally covered by the ADI. The present procedure therefore provides an acceptable margin of safety to the entire population for those pesticides with complete data bases. The advantage of providing separate ADIs for different age (or physiological) groups of the population, would therefore be limited to indicating those groups who may be in a reduced-risk category, rather than indicating those at increased risk.

A document entitled "Guidelines for Predicting Dietary Intake of Pesticide Residues" was published by WHO in 1989 [177]. This document provides guidance on the prediction of the dietary intake of residues of a pesticide for the purpose of comparison with the ADI allocated by JMPR. The document recommends a step-wise approach to predicting intake, considering average consumption of the treated commodities and a number of factors (such as processing, variations in residues level with time and the percentage of a given commodity that is treated) that usually have the effect of providing a more accurate prediction of real pesticide residue intake. An example of dietary intake calculations for a hypothetical pesticide is given in Chapter 3 of "Guidelines for Predicting Dietary Intake of Pesticide Residues."