験，例えば変異原性試験等が要求される。

最も適切な試験から得られたNOAELを適切な安全係数で割ることによりADIを決定する。最も低いNOAELが必ずしもADI設定のもとになっているわけではない（第8.2.1項参照）。したがって，慢性毒性試験から得られたNOAELが生殖試験から得られたNOAELより低い場合であっても安全係数をより高く取ることにより（第9.2項参照），後者のNOAELをADI設定に使うこともある。この考え方に基づくと，ヒトの全年齢範囲をこのADIでカバーできる。したがって，完全なデータベースを持つ農薬について現在の方法を当てはめると，全人口に対する許容可能な安全域を設定できる。これ故，異なる年齢（または生理学的）のグループにそれぞれ別々のADIを割り当てることは，むしろ危害の高いカテゴリーではなく，危害の低いカテゴリーに入っていることを示すこととなり，利点は限られる。

1989年に“食品経由の残留農薬摂取量予測に関するガイドライン”と題された文書がWHOから発行された［177］。この文書はJMPRによって設定されたADIと比較検討することを目的とし，農薬残留物の食品経由の摂取量の予測に関する指針を提示している。この文書は，農薬処理された農産物の平均摂取量及び残留農薬の実質摂取量のより正確な予測を行う際に通常影響を与える多くの要因（例えば，加工，残留量の時間変動及び農薬で処理された農産物の割合等）について考慮し，段階的に摂取量の予測を行うよう提案している。ある農薬を仮想した摂取量の計算については“食品経由の残留農薬摂取量予測に関するガイドライン”の第3章に記載されている。

9. EVALUATION OF DATA

9.1 Extrapolation of Animal Data to Humans

The objective of the safety evaluation of pesticide residues in food is to determine the maximum daily intake of the pesticide that will not result in adverse effects at any stage in the human lifespan. Since, in the majority of cases, data on humans are inadequate to permit such a determination, effects observed in other species must be extrapolated to humans. Ideally, data on comparative pharmacokinetics, metabolism, and mechanism of action should be utilized in the extrapolation. However, such data are not available in the majority of cases. The use of relevant biomarkers of exposure and effect such as the formation of adducts to DNA or blood proteins like haemoglobin in humans and test animals may also be useful in the extrapolation across species. Further research in this area is to be encouraged.

Three basic approaches are now generally used in the extrapolation of the results of studies in experimental animals to humans: the use of safety factors, the use of pharmacokinetic extrapolation (widely used in the safety evaluation of pharmaceuticals), or the use of linear low-dose extrapolation models.

JMPR has not utilized the third approach (the use of linear low-dose extrapolation models). A number of these models have been used to determine the "virtually safe dose" (VSD) of carcinogens for humans. One major drawback of these models is the lack of consideration of many of the biological factors which should be taken into account. Furthermore, the Various mathematical models available (Probit, Wiebel, etc.), when applied to the same data, can result in VSD values which vary by orders of magnitude. There is no agreement among toxicologists on the "best" mathematical model available today, nor on whether these mathematical models have any biological meaning at all.

Pharmacokinetic extrapolation requires human pharmacokinetic data, which are rarely available for pesticides. The method involves a comparison of pharmacokinetics in human and experimental animals. The relative sensitivity of receptor sites must also be taken into consideration.

The JMPR approach has generally been limited to the first of the three approaches, that is the use of safety factors. These are applied to the NOAEL determined from the experimental animal data, or preferably, from data in humans, if available.

9.2 Safety Factors

9.2.1 Background

The 1963 JMPR adopted the commonly used empirical approach for the extrapolation of data to man, i.e. "the maximum no-effect dietary level obtained in animal experiments, expressed in mg/kg body weight per day, was divided by a 'factor', generally 100." [35, p. 11]. This concept appears to have been adopted from the report of the second JECFA Meeting which states that ". . . a dosage level can be established that causes no demonstrable effects in the animals used. In the extrapolation of this figure to man, some margin of safety is desirable to allow for any species differences in susceptibility, the numerical differences between the test animals and the human population exposed to the hazard, the greater variety of complicating disease processes in the human population, the difficulty of estimating the human intake, and the possibility of synergistic action among food additives." [31, p. 17]. The Committee then stated that the 100-fold margin of safety applied to the maximum ineffective dose (expressed in mg/kg body weight per day) was believed to be an adequate factor.

The 1965 JMPR [36] discussed the concept of the acceptable daily intake and safety factors. It noted that the 100-fold factor could be modified according to circumstances (e.g., reduction to 10 or 20 fold when human data are available or in the case of well-studied organophosphates). The 1966 JMPR indicated that when a temporary ADI was allocated, the margin of safety applied to the NOAEL derived from experimental animal data should be increased [38]. These principles were applied by the 1966 Joint Meeting when establishing a temporary ADI for pyrethrin (safety factor of 250) [39].

A WHO Scientific Group considered safety factors in 1967 [169]. This Group noted that safety factors could be varied and described circumstances where increased safety factors should be used. These included toxicological data gaps and when it was necessary to establish temporary ADIs. Decreasing the margin of safety was proposed when pertinent biological data indicates uniform species response, when the initial effect is clear-cut and reversible, or when cholinesterase inhibition or adaptive liver enlargement is the initial effect. Otherwise a 100-fold safety factor was considered to be a useful guide.

The 1968 JMPR [42] indicated that, where human data comprised the basis for the NOAEL used in determining the ADI, a smaller safety factor might be utilized. This statement was amplified by the 1969 JMPR [44] to include human biochemical as well as toxicological data as justification for reducing safety factors.

The 1975 JMPR, in addressing the question of safety factors in toxicological evaluation, stated that:

"It should be emphasized that the magnitude of the margin of safety applied in each individual case is based on the evaluation of all available data. In consideration of any information that gives rise to particular concern, the magnitude of the margin of safety will be increased. Where the data provide an assurance of safety, the magnitude may be decreased. Therefore, it is impossible to recommend fixed

rules for the margin of safety to be applied in all instances." [54, p. 9].

In 1977, the JMPR "wished to clarify the situation regarding safety factors in arriving at ADIS for man. The establishment of the ADI for man is not a simple arithmetic exercise based on the no-effect level, as the safety factor may vary widely from one compound to another. Although safety factors are determined empirically, they are dependent on the nature of the compound, the amount, nature and quality of the toxicological data available, the nature of the toxic effects of the compound, whether the ADI or TADI for man is established, and the nature of any further data required." [57, p. 4].

During a discussion on general principles used by the JMPR, the 1984 Meeting [72] stressed the degree of uncertainty that accompanies a toxicological evaluation, and stated:

"The use of variable safety factors by the JMPR in the estimation of ADI values reflects this uncertainty, and underlines the complexity of assessing the human health hazards of pesticides. No hard and fast rules can be made with regard to the magnitude of this safety factor, since many aspects have to be considered, such as species differences, individual variations, incompleteness of available data, and a number of other matters such as considerations of the fact that pesticide residues may be ingested by people of all ages throughout the whole life-span, that they are eaten by the sick and the healthy as well as children, and that there are wide variations in individual dietary patterns." [72, p. 3].

The original concept of the use of 100-fold safety factors was based on interspecies and intraspecies variations [114]. Included in this consideration were variations between strains, provision for sensitive human population sub-groups, and possible synergistic effects due to exposure to more than one chemical.

The 100-fold safety factor can be viewed as two 10-fold factors, one for inter- and one for intra-species variability [111]. While these safety factors appear, on the basis of experience, to provide adequate margins of safety in the extrapolation of data to man, they may, of course, be questioned. Some experimental support for safety factors was published by Dourson & Stara [261 in 1983. This paper also proposed an additional 10-fold factor for extrapolating sub-chronic data, and for converting lowest-observed-adverse-effect levels to NOAELs (factors of 1-10, depending upon the severity and concern raised by the observed effect). Additional clinical and epidemiological research may improve the characterization of the variation in response within the human population to various pesticides and may allow a more accurate determination of safety factors.

9.2.2 Principles