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Significance of Excursions of Intake above the Acceptable Daily Intake (ADI)

Report of a Workshop held in April 1998

Organised by ILSI Europe Acceptable Daily Intake Task Force and Food Chemical Intake Task Force

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Report of a Workshop on the Significance of Excursions of Intake above the Acceptable Daily Intake (ADI)

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BACKGROUND

The Acceptable Daily Intake (ADI) for humans was originally developed in the Joint FAO / WHO Expert Committee on Food Additives (JECFA) and 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" (WHO 1987). JECFA has not provided any firm guidance on how to evaluate excursions of intake above the ADI, but WHO in 1987 stated that "because in most cases, data are extrapolated from lifetime animal studies, the ADI relates to lifetime use and provides a margin of safety large enough for toxicologists not to be particularly concerned about short-term use at exposure levels exceeding the ADI, providing the average intake over longer periods of time does not exceed it" (WHO 1987).

In discussing short-term intakes in excess of recommended limits, JECFA in 1989 concluded that short-term exposures at levels exceeding the Provisional Tolerable Weekly Intake (PTWI) for a contaminant is not a cause of concern, provided that the individual's intake averaged over longer periods of time does not exceed the level set. JECFA also stated that it was impossible to make a generalisation concerning the length of time during which intakes in excess of the PTWI would be toxicologically detrimental. Any detrimental effect would depend on the nature of the toxicity and the biological half-life of the chemical concerned. JECFA considered that intakes of food additives in excess of the ADI are less likely to occur and easier to control than in the case of contaminants which are allocated either a PTWI (WHO 1989) or a Tolerable Daily Intake (TDI) (WHO 1987).

The ILSI Europe Acceptable Daily Intake Task Force together with the ILSI Europe Food Chemical Intake Task Force initiated a workshop which took place from 21–23 April 1998 in Milan, Italy, to help identify what information would be needed, with what precision, and what is already available to evaluate the significance of excursions of intake above the ADI. The specific aims of the workshop were to address the following questions:

- By how much can the ADI be exceeded?
- For how long can excursions above the ADI be tolerated with respect to chronic toxicity, accumulation, and mechanisms of toxicity?
- What methods should be used to estimate intakes so that the estimates are relevant to the ADI?
- Do the same principles apply to contaminants that have TDI or PTWI values?

GENERAL INTRODUCTION

Dr. S. Barlow (Brighton, United Kingdom) gave an overview of the workshop and reminded the participants that little scientific attention has been paid to the significance of excursions of intake above the ADI, and that no international guidelines have ever been provided to help risk assessors and risk managers make decisions in this area. One reason may be the perception that average intake levels are well below the ADI for most additives and residues. Intake/ADI comparisons are now required by several EU directives, as well as being requested by the Codex Alimentarius Commission for certain colours, and Dr Barlow stated that there is now a need for scientifically based guidelines.

Dr. Barlow also stated that the significance of excursions of intake above the ADI for any individual chemical may need to be assessed on a case-by-case basis. Worst-case estimates indicate that the average intakes of some food additives, residues, and contaminants are well below the ADI. However, for some compounds excursions above the ADI may occur.

Dr. Barlow stressed that there are difficulties in measuring actual intakes and in interpreting the data obtained. She pointed out that questions such as "How precise is the ADI?" and "How precise are intake data?" or "What percentage of the population should be protected?" are frequently asked but that generally no clear answers are provided.

DERIVATION AND PRECISION OF THE ADI

Dr. M. Younes (Geneva, Switzerland) explained that JECFA and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) allocate ADIs to food additives, pesticides, and veterinary drugs that exhibit thresholds of toxicity. For contaminants, JECFA derives Tolerable Intakes, which are expressed on either a daily or a weekly basis. Contaminants that are not known to accumulate in the body are assigned Provisional Maximum Tolerable Daily Intakes (PMTDIs), whereas PTWIs are established for contaminants that may accumulate in the body. The U.S. Environmental Protection Agency (US EPA) establishes Reference Doses (RfDs) for environmental chemicals, and the International Programme on Chemical Safety (IPCS) in its Environmental Health Criteria monographs derives TDIs. The derivation of reference doses and tolerable intakes is equivalent to the derivation of the ADI by JECFA and JMPR.

Dr Younes made a distinction between a formal risk assessment and the derivation of an ADI. The risk assessment, which consists of hazard identification, hazard characterisation (dose-response assessment), exposure assessment, and risk characterisation, aims to characterise the risk (expected frequency of occurrence of harm) within defined exposure conditions, whereas the approach for setting ADIs and TDIs should be regarded as a safety assurance, which defines exposure limits below which no harmful effects would be expected.

For the establishment of the ADI, a no-observed-adverse-effect level (NOAEL) is identified for the critical effect in the pivotal study, to which an appropriate safety or uncertainty factor is applied to data from experimental animals. By default, a factor of 100 is used when the database is considered adequate (a 10-fold factor to allow for differences between test species and humans and a 10-fold factor to allow for human variability). In toxicological studies, doses are usually spread over wide intervals. Thus, the NOAEL may be considerably less than a marginally effective dose. Traditionally, use has not been made of the dose-response relationship when establishing ADIs, but Dr. Younes encouraged increased use of modelling methods, such as benchmark dose analysis or probabilistic methods, which consider all available dose-response data.

Dr. Younes considered it unlikely that consumption at the level of the ADI for food additives, pesticide residues, and veterinary drug residues would result in significant risk to the consumer because of the conservatism built into it. However, tolerable intakes for contaminants present in the environment at high levels are often based on less optimal databases. Moreover, smaller than standard safety factors are sometimes used to prevent parts of the food supply from being destroyed on safety grounds.

Professor E. Dybing (Oslo, Norway) explained that toxicokinetic and toxicodynamic variability may help to explain interindividual differences in susceptibility in exposed populations. Toxicokinetics and toxicodynamics may be influenced by a variety of factors. For example, absorption of chemicals may increase with age, and because of changes in blood flow the clearance of most drugs increases during pregnancy. In the elderly, decreased renal and hepatic excretion, reduced serum protein binding, and reduced volume of distribution may enhance chemically induced effects. Gastrointestinal disease, liver disease, and kidney disease may lead to enhanced toxic responses to chemicals. Genetic polymorphism affecting metabolising enzymes can also influence toxic responses. In the developing conceptus some cells and tissues are exquisitely sensitive to chemical exposures, and organs and tissues of newborns and very young children may also show enhanced sensitivity. Professor Dybing considered the default uncertainty factor of 100 to be protective for age differences and most, but possibly not all, disease states, and therefore a review on a case-by-case basis was needed.

Dr. G.J.A. Speijers (Bilthoven, The Netherlands) discussed the factors influencing the precision of the ADI (and TDI and PTWI). Although human data on the toxicity of a chemical are preferred for the safety evaluation, they are frequently lacking or are incomplete. Usually, hazard characterisation is based on experimental animal studies. Because the ADI predicts a safe intake level for life-span exposure, the toxicological database should include long-term studies to establish the NOAEL. The precision of the ADI greatly depends on the precision of the toxicological studies considered.

In relation to the significance of incidental intake excursions above the ADI, Dr. Speijers concluded that because of the variation in the precision of the experiments, a slight incidental excursion would not lead to an increased risk. However, it was not possible to provide a general guideline on its permissible duration and magnitude, and for short-term excursions, the ADI may not be the appropriate figure on which to base the evaluation, because it may overestimate the risk.

METHODOLOGY AND PRECISION OF INTAKE STUDIES

Professor M. Gibney (Dublin, Ireland) gave an overview of dietary intake methods. Food consumption data can be classified as direct (survey-based methods) or indirect (using economically derived indicators such as the household budget approach). The indirect approach can be either assumed (hypothetical) or actual. An example of an indirect hypothetical/theoretical approach is the Budget Method. The indirect actual estimates use household budget data or food balance sheets. The indirect methods are inexpensive and provide reliable time trends but provide no individual data and no consumer-only data and therefore are of limited value in measuring food additive intake. However, Professor Gibney was of the opinion that, if the use of a crude, worst-case approach did not indicate that the ADI was being exceeded, there was no need to waste resources on refined intake estimates of that particular additive.

The direct methods can be classified as quantitative or qualitative. The most often used qualitative method is a food frequency questionnaire (FFQ), because it is inexpensive and can accommodate large sample sizes. FFQ is limited in its applicability to additive intake studies but can be used to determine the proportion of a population who are consumers. Direct quantitative studies can be classified as either retrospective (24-hour recall, dietary history) or prospective (weighed intake, dietary records). The utility of a food consumption study for the estimation of food additive intake is influenced by the duration of the study. As duration is extended, the population intake remains unchanged and the proportion who are consumers increases, whereas the average intake among consumers-only falls. The utility of the study is also influenced by the degree of details retained within the database. Such studies, e.g., a 14-day diary plus a FFQ, are very costly, and if they are to be used for assessment of excursions above the ADI, this should be built into the design and carefully planned. The question of under- and overreporters and the consequence for estimates of extreme intakes should also be addressed.

Professor Gibney considered a 3-day diary plus a FFQ a compromise approach. He considered the minimum group size for an appropriate study to be 200 subjects. The 3-day FFQ can be used to estimate the true proportion of consumers.

Dr. P. Verger (Paris, France) stressed that the aim of the exposure assessment is to identify groups potentially at risk because of high intake by comparing an estimated daily intake with an ADI or a TDI. Although an individual dietary record conducted during 1 week combined with the use of a representative sample of the population in practice might be the most precise study to perform, the ADI of a chemical relates to lifetime intake; however, in general nobody is “at risk” of excessive intake over a lifetime.

The procedure most often used is to determine the distribution of the consumption in the general population followed by *a priori* identification of groups potentially at risk, such as infants and children, pregnant women, the elderly, diabetics, and vegetarians. In France, a step-by-step procedure has been used for several food additives initially selected by the Budget Method. A large food consumption database was used and the data corrected for home production and consumption outside the home. Using sulfites as an example, Dr. Verger explained that when it was assumed that the maximum authorised levels of additives were used in all food categories, the result indicated that the calculated theoretical maximum daily intake of sulfites would exceed

the ADI of 0.7 mg / kg body weight (bw) / day for approximately half the French population. It was estimated that about 10% of the population exceed the ADI by more than three times. When a corrected evaluation was performed using real levels of sulfite use, the estimated mean intake was about twofold lower. Dr Verger illustrated the efficiency of the *a priori* approach for identifying potentially at-risk groups using examples of increased exposure to aspartame for diabetic children and low calcium intake for vegetarians.

Dr. C.A. Lawrie (London, United Kingdom) discussed the precision and accuracy of intake estimates for food chemicals and pointed out that, not unexpectedly, there is an inverse relationship between the accuracy of an estimate and the time and effort required to produce it. As a general principle, initial estimates using relatively crude methods that are designed to be conservative and that overestimate the "true" intake should be performed, and only if the results are not sufficiently reassuring should the estimate be refined.

The most common method for estimating food chemical intake is to combine information on the consumption of the foods in which the substance is likely to be present with quantitative data on its concentration. The default assumption is often that the food additive is present in the food at its maximum permitted concentration. The accuracy of intake estimates is affected by food coding (complexity versus cost and reliability) and inclusion of brand data, size of portion consumed, and duration and size of study. Using banana intake as an example, Dr. Lawrie showed that a 1-day study on the intake of the average consumer resulted in an estimate of 99 g / day whereas a 7-day study would find 29 g / day, and the intake of a high-level consumer would drop from 250 g / day to 100 g / day going from 1 to 7 days. A 4-day study would yield figures closer to the 7 day figures.

The most precise assessment of intake by individual consumers involves either a direct analysis of the food being consumed (duplicate diets) or an *in vivo* measure (biomarker) such as the excretion of the substance and / or breakdown products in urine. The use of urinary biomarkers was illustrated by UK studies on acesulfame K and saccharin which showed that the frequency distribution of consumers obtained by measuring urinary acesulfame K was in good agreement with that obtained from a diary record of selected foods. However, the measurement of urinary saccharin produced higher frequencies than those obtained by a dietary record, probably reflecting sources other than foods, such as pharmaceuticals.

CONSEQUENCES OF EXCEEDING THE ADI

Issues related to duration of exposure

Professor R. Walker (Surrey, United Kingdom) stressed that the significance of excursions above the ADI, TDI, or PTWI can be assessed only by reference to the database that led to their derivation, particularly the duration of the pivotal study (chronic, subchronic, acute), the pharmacokinetic parameters, and the nature of the toxicity and mechanism of action. Although this implies a case-by-case assessment, he identified a number of typical situations:

For substances, usually contaminants, having very long half-lives leading to accumulation in target organs/tissues, chronic toxicity is most often manifested when critical concentrations are achieved in these tissues, and there are large differences between the acutely toxic doses and the chronic NOAELs. In such cases, the setting of a PTWI is best practice and peak excursions of several times the PTWI for relatively short periods (days, weeks, or even months) or lower peak intakes for even longer periods (months to years) may be of no consequence provided that the integrated exposure over longer periods does not lead to critical steady-state tissue concentrations.

A more common situation for food additives is where the ADI is based on a chronic study but the half-life is short; i.e., the situation is one of chronic stress rather than cumulative toxicity. In such cases, the effects on the target organ can usually be identified in subchronic studies. Consequently, if the effects seen at the lowest-observed-adverse-effect level (LOAEL) in subacute/chronic studies are reversible, short-term studies with reversibility demonstrated may become pivotal in assessing the consequences of short-term excursions above the ADI. If the short-term effects are not fully reversible, or are even progressive, the significance of short-term peaks of intake above the ADI could depend on careful evaluation of the NOAEL or LOAEL from subacute or subchronic studies.

In some cases where the ADI is based on a chronic toxicity study but the margins between the chronic NOAEL and some aspects of acute toxicity, e.g., teratogenicity, may be small, the acute NOAEL could be used appropriately to evaluate the risk associated with short-term peaks of exposure.

Although not comprehensive, these cases could provide a framework against which to discuss the potential effects of excursions above the ADI and to reach rational conclusions not based on the misapprehension that the ADI (or even worse, the PTWI divided by seven) is a lower bound of toxicity.

Dr. F. Sullivan (Brighton, United Kingdom) outlined the differences in the temporal equivalence between experimental animals and humans for developmental toxicity (limited to teratogenicity) and stated that teratogenic effects of chemicals are dose and time related, and that in general there is a threshold dose below which teratogenic effects will not be produced. Chemicals which produce teratogenic effects in animals have ADI values which are far below the teratogenic dose. As the dose increases, it is very unusual for teratogenicity to be the first effect seen, and multigeneration studies provide sensitive NOAELs on reversible effects, such as reduced pup weight. Dr. Sullivan therefore found it highly unlikely that excursions above the ADI would produce teratogenicity. However, some teratogens act only if a sufficiently high peak level is achieved in the blood and embryo, whereas the effect of other teratogens is more influenced by the area under the blood concentration/time curve.

Dr. I. Knudsen (Søborg, Denmark), as a result of his examinations of temporal equivalence between test species and humans in general toxicity issues, concluded that the animal lifetime study was the most relevant and most important instrument for the toxicological safety assessment, because the biology of the total lifetime best matches the qualitative and quantitative challenges of life from one species to another. He found that temporal equivalence for shorter intervals could not be established easily because of the large differences in genetic timing of different life stages between species. However, this did not exclude the importance of specific toxicological studies, e.g., reproduction/teratology studies, as they might identify a sensitive stage and therefore become the pivotal study for the safety assessment.

Professor A. Renwick (Southampton, United Kingdom) explained that an increased risk of an adverse effect following intakes of food chemicals above the ADI/TDI would occur only if they were of sufficient duration to produce an intake-related and proportional increase in intracellular concentrations of the active chemical (toxicokinetics) and were able to produce the cellular changes which result in the toxic response (toxicodynamics).

Compounds assigned an ADI are assumed to show thresholds. The time necessary for the expression of a toxic response *in vivo* depends on the nature of the toxic processes resulting from the presence of a "toxic" body load and on the time required to achieve a steady-state body load. The interpretation of the possibility for adverse effects at intakes above the ADI have to be considered in relation to effects produced in animals at doses above the NOAEL. In general, our understanding of the time course of toxicodynamic processes leading to adverse effects is much better for acute effects than for subchronic and chronic threshold effects. Reversibility is important for consideration of transient intakes above the ADI, because the consequence of a reversible effect could be minimised by a subsequent period of exposure at the ADI. The doses associated with acute effects in animals are usually, but not always, higher than those for chronic toxicity. For reversible effects, short periods of intake above the ADI may be of significance only if the magnitude of the intake is sufficient to erode a 100-fold safety margin (uncertainty factor) for acute effects in animal experiments.

However, safety assessment and the determination of ADI/TDI values are usually based on adverse effects detected in subchronic or chronic toxicity studies. Such studies are of sufficient duration for the body load and blood concentration of the compound to reach steady state, at which time the daily dose is balanced by an equal rate of elimination. Once a steady-state "nontoxic" body load has been established by continued daily intake at or below the ADI, the change in body load for an increase in daily intake depends on the magnitude of the change in intake, the initial body load, and the duration of intake in relation to the half-life of the compound. The time to reach a new steady state following an increase in daily dose depends on the terminal half-life of the compound. The proportions of the new steady-state values at one, two, three, and four half-lives after a change in dose (either an increase or a decrease) are 0.5, 0.75, 0.875, and 0.9375, suggesting that an intake of twice the ADI would not result in blood (or plasma) concentrations twofold above those at the ADI unless the period over which the intake exceeds the ADI is about four to five times the half-life.

Dr. M.H.R. Löwik (Zeist, The Netherlands) stated that the proper use of food consumption data for risk assessment of food additives is very complex. One of the confounding factors is the influence of the time frame of the assessment on the outcome of dietary intake estimates. Central to this time dependency is the within-subject variation regarding the use of food products. Short-term habits arise as a result of, e.g., different consumption on weekends and weekdays, eating out, holidays abroad, seasonality, and age of subject. He reminded the audience that food

consumption data collection takes place at a single point in the subject's life during a very short period of time (normally 1–7 days, seldom for a month), and therefore the survey data based on 1 day refer to only 0.004% of an average lifetime. Within-subject variation is normally as large or larger than between-subject variation and in general is greater at a younger age. He gave examples of within-subject variations for separate age-sex groups and concluded that corrections for within-subject variation based on figures found for the total population will be too small and may, for instance, underestimate variability in consumption in younger age groups. He suggested that corrections for within-subject variation be based on separate homogeneous groups.

Based on a demographic picture of the population, a reasonable approximation of lifetime intake can be obtained. For The Netherlands, a 2-day record for age-gender groups was used to estimate that the daily consumption of food ranged from 15 to 140 g/kg bw. The mean value was estimated to be 45 g/kg bw. These and other characteristics of dietary exposure can be calculated for food groups and even individual foods. The proportion of users and the consumption levels among users depend on the time frame of the assessment, especially for irregularly consumed products, where the proportion of users will be higher and the intake levels will be lower when the time frame is longer. The use of only 2-day records overestimates lifetime exposure and Dr Löwik suggested that records of 14 days and longer duration would be needed to estimate lifetime exposures to commonly used ingredients.

Issues related to magnitude of exposure

Dr. M. Dourson (Cincinnati, USA) introduced categorical regression as a tool to estimate potential health risk from chemical exposure. It is a mathematical tool to regress ordered categories of toxic severity (e.g., NOAEL, LOAEL, or pathological staging) on dose, and the method can estimate the likelihood of observing any of the categories of severity at any dose level. The categorisation requires toxicological judgement in estimating and ranking severity of all endpoints under consideration. This provides a consistent basis for calculating risk above the RfD or ADI. However, animal-to-human extrapolations are still needed. The use of categorical regression was illustrated using toxicity data on aldicarb. The data came from human clinical studies, dietary exposures in experimental animals, and accidental human exposure from contaminated crops. The result of using data from human clinical studies suggested a maximum-likelihood risk estimate of adverse effects (neurotoxicity) of 0.008% at a 10-fold higher dose than the US EPA RfD of 0.001 mg/kg bw established on the basis of inhibition of acetylcholinesterase activity in human blood. When blood cholinesterase inhibition of 20% or more was considered an adverse effect, a maximum-likelihood estimate of adverse effects was 0.1% at a dose 10-fold higher the RfD.

Professor A. Renwick (Southampton, United Kingdom) explained that an excursion of intake above the ADI theoretically moves the most sensitive individuals from negligible risk to possible risk and, likewise, the population distribution of internal dose towards the dose-response curve. The proportion of the population affected depends on the magnitude of the excess intake, the difference between the NOAEL and the threshold for toxicity in animals, and the variability in the kinetic parameters which determine the internal dose in humans. The severity of any effect in sensitive and high-intake individuals depends on the magnitude of the excess intake, the nature of the critical effect, and the slope of the dose-response curve. He assumed that the effect in animals at the LOAEL is relevant to humans and that the dose-response relationship for different adverse effects above the LOAEL in animals would be of the same order as that for humans. Therefore, when humans are protected by the NOAEL of the most sensitive effect, they also will be protected against other endpoints.

The NOAEL could be several times lower than the LOAEL. The actual threshold for biological effect will be between the NOAEL and the LOAEL. The threshold:NOAEL ratio corresponds to an extra safety factor in addition to that normally applied to a NOAEL. Renwick (1993) has proposed that each of the 10-fold safety factors conventionally applied to the NOAEL to cover interspecies and interindividual differences should be subdivided into kinetic and dynamic factors, and these were slightly revised by WHO (1994) such that the 10 x 10 factor should be considered as (4 x 2.5) x (3.16 x 3.16). Theoretically, there could be a low incidence of individuals with toxicokinetic variability that exceeds the default uncertainty factor of 3.16 (for kinetics). However, the incidence of individuals who would exceed both 3.16-fold factors (for kinetics and dynamics) is extremely low. The severity of effect for individuals not covered by the residual uncertainty factor for human variability can be assessed only by comparison to the data for the critical effect in animals, with the assumption that the slope of the dose-response curve will be similar in both species.

MODELLING OF INTAKE AND RISK

Dr. M. Chambolle (Paris, France) discussed methods to identify and characterise populations of extreme consumers over long periods. It is seldom possible to obtain original data on the intakes of food constituents, which have to be evaluated from data on food intake. Food consumption studies are generally performed over a period of days, typically no more than 3 or 4 consecutive days. The principal use of dietary recall is to describe the average dietary intake of groups and not of individuals, and food frequency questionnaire (FFQ) methods are better suited for ranking subjects according to food intake than for estimating levels of intake. Thus, the usual methods for the assessment of dietary intake are not fitted to estimate chronic intakes of foods.

When the distribution of intakes is available, different percentiles are used by different countries to characterise extreme consumers. Although these are essentially political decisions, Dr. Chambolle mentioned that when consumers were able to choose their own level of intake (e.g., for food additives, which are declared on the labels) the 95th percentile level often was regarded as acceptable, but in the case of contaminants, the 99th percentile level was often considered more appropriate. However, when the precision of such estimates is taken into consideration, studies have shown that the apparent improvement in risk control by moving from the 95th to the 97.5th percentile level in many cases was questionable. He considered the 95th percentile level a good compromise between a high level of protection and precision in the estimates of intakes.

Dr. Chambolle pointed out that several studies have shown that it is possible with some confidence to estimate extreme intakes from mean intakes. When consumers-only are considered, a rather constant ratio of about three has been found between the mean food intake and the 95th percentile of consumption of particular foods, whatever the proportion of consumers within the general population. However, if only data of mean intakes for the total population are available, estimation of intakes at higher percentiles is much more difficult.

Dr. Chambolle also mentioned that the characteristic of an extreme consumer is one who is a regular, even daily, consumer and does not necessarily have a very high daily intake. Therefore, he advised complementing short-term food intake studies by a FFQ, which could help identify the

regular consumer. A first step towards identifying possible target groups is to determine the categories (households) where extreme consumers are overrepresented. Finally, he stated that generation trends should be taken into account when predictions of future levels of intake are attempted from present intakes.

Dr. D. Tennant (London, United Kingdom) stressed that when estimating acute intakes of chemicals in food, one must take great care to ensure that the period over which intake is estimated corresponds to the toxicological endpoint of concern. The concentrations of certain chemicals in food, such as pesticide residues, may show extremely wide unit-to-unit variations (as discussed by Dr. Harris), so that a single very high intake is possible. For single (acute) intakes, comparison to an ADI based on chronic data would greatly overestimate the risk. In such circumstances, acute reference doses should be estimated and compared to the specific acute exposure data. This concept is accepted by JMPR.

Several techniques are available for estimating acute intakes of chemicals from food, the simplest being to create estimates from one large portion of a single food and assume it contains the chemical of concern at the maximum level. Such methods may provide useful screening estimates. A better choice would be to use probabilistic techniques, such as the Monte Carlo model. Great care must be used when interpreting such statistics, because uncertainty in the data increases considerably in the upper tail of the distribution and errors tend to exaggerate true levels of risk. Other approaches to estimating intake could include market share, review of subgroups, and of the actual consumer rather than the whole population.

Dr. A. Jarabek (Research Triangle Park, USA) provided examples of the use of a Bayesian approach for estimating the risk associated with intake above RfD levels, using aldicarb and toluene as examples. With aldicarb she outlined the procedure used to compute a posterior distribution from a likelihood function and a prior distribution based on the frequency of responders with clinical signs and blood cholinesterase inhibition found in studies. These distributions could be used to estimate the probability of persons expected to respond with symptoms following ingestion of a given dose of aldicarb.

Dr. P. Price (Portland, USA) discussed basic concepts in dose-response modelling and presented an approach using Monte Carlo techniques for modelling response rates at doses above the ADI. The approach uses a linear threshold (hockey stick) model of response and is based on the current system of uncertainty factors for inter-species (UF_A) and intra-species (UF_H) differences. The model uses the ADI as a measure of a zero (or minimal) risk in humans (ED_0) and the animal ED_{50} (based on all adverse effects in the test animals) divided by the UF_A as a model to predict the dose that causes an effect in a typical human (ED_{50}). Finally, a linear model is used as an upper bound to the actual dose-response for doses between the ED_0 and the ED_{50} in humans. The model thus can produce quantitative estimates of risk (dose-response) by randomly selecting values for UF_A and UF_H and calculating a response to the dose. The process is repeated several thousand times, and a range of response values is produced for each dose. The analysis is independent of the actual dose-response curve, and is conservative (linear model assumption).

Professor A. Boobis (London, United Kingdom), discussing high-dose linearity / nonlinearity, explained that as exposure increases in experimental animals, almost all of the processes underlying the kinetics and metabolism of a compound will approach saturation, depending on the affinity of the binding sites involved. Plasma and tissue protein binding are dose dependent, and saturation would probably occur at higher doses than saturation of enzymes and transporters. Nonlinearity will be common in animal studies where high doses are used but rare

following human intake at the ADI level. Human intakes that do result in nonlinear kinetics will more likely be in relation to active cellular uptake, metabolism, and secretory transport of compounds. The consequences for human health will depend on whether the toxic effect of the compound is due to the parent or a metabolite. Saturation of the enzymes responsible for formation of a toxic metabolite would diminish its potential toxicity, whereas saturation of a detoxification pathway would be potentially detrimental. The long-term consequences of such saturation would depend on the rate of elimination of the compound.

CASE STUDIES

Food additives

Monosodium glutamate (MSG) was used as a case history for a food additive, although it has been allocated an ADI "not specified". The question was whether high acute intakes might arise that could invalidate the assumption of safety at all foreseeable levels of exposure in food additive use. Referring to the toxicological database, Professor R. Walker (Surrey, United Kingdom) considered the potential effects (neuronal damage) in babies of high exposure peaks and the role of MSG in the so-called Chinese restaurant syndrome as the critical issues for evaluation. In light of the toxicological studies, human metabolic studies in neonates and adults, the physiological and nutritional role of MSG, and the fact that use of the food additive does not markedly increase the total dietary burden, Professor Walker concluded that no foreseeable circumstances would arise in which intakes would be such as to invalidate the appropriateness of allocating an ADI not specified.

Pesticides

Dr. C. Harris (York, United Kingdom) presented a study on the assessment of risk of acute toxicity associated with cholinesterase inhibition in children 1.5 to 4.5 years old (toddlers) from residues of carbaryl in apples and triazophos in apples and carrots. Initially, studies had shown great variability of triazophos in individual carrots (highest residue levels could be 25 times the mean level in bulked samples). This was followed up by a comprehensive study on the variations in individual residue levels of organophosphate pesticides in a number of unwashed crops. Applying conventional point estimates using levels of high consumption during a single day, and assuming that the relevant food items were contaminated with the highest levels, indicated that the acute RfDs for carbaryl and triazophos could be exceeded in toddlers by more than 200% if crops were unwashed. To obtain a more realistic picture of the risk of exceeding the RfD, a probabilistic assessment of toddlers' exposure to these pesticides was performed using Latin Hypercube techniques. The consumption of food items (obtained from food consumption surveys), the residues of pesticides in food (measured), and individual body weights (sampled

from survey data) were all presented as continuous probability distributions. These input variables were sampled and a probability distribution for pesticide intake was produced. With these techniques the probability of intake above the RfD was estimated at 0.29–0.86% for carbaryl in apples and at 2.35–4.28% for triazophos in apples and carrots. In addition, the probability of triazophos intake exceeding 10 times the RfD was estimated to be 0.20–1.00%.

Contaminants

Using polychlorinated dibenzodioxins and dibenzofurans ("dioxins") as examples of contaminants having very long half-lives in humans, Dr. F. Pollitt (London, United Kingdom) discussed the implications of exceeding the TDI, particularly in the context of high intakes by breast-fed infants. For the most toxic congener, 2,3,7,8-TCDD, a TDI of 10 pg/kg bw had been established based on results from multigeneration and chronic toxicity and carcinogenicity studies in rats. A revised TDI of 1–4 pg/kg bw has been proposed since this paper was presented. To estimate the combined toxicity of mixtures of dioxins, TCDD equivalents have been assigned to the other dioxins and are used to compute a composite 2,3,7,8-TCDD toxic equivalence (TEQ) intake that can be related to the TDI. The upper-bound dietary intake of dioxins by the average UK adult consumer was estimated at 2.4 pg TEQ/kg bw/day for 1992. However, owing to the accumulation of dioxins in human adipose tissue, including mother's milk, the estimated intake of dioxins by breast-fed babies was estimated as 170 pg TEQ/kg bw/day at 2 months of age, falling to 39 pg TEQ/kg bw/day at 10 months of age.

The appropriate dosimetric for the toxic effects of the dioxins is the body burden rather than the daily intake. The steady-state body burden at the TDI of 10 pg/kg bw is estimated to be approximately 45 ng TEQ/kg bw assuming that the half-life of all congeners contributing to the TEQ is 9 years. Dr. Pollitt presented calculations that showed that breast-feeding is predicted to result in a higher body burden of dioxins in early life but not in an increase in the ultimate steady-state body burden, compared with that resulting from ingestion of the TDI from birth. For congeners with shorter half-lives, e.g., 1–3 years, breast-feeding will lead to high body burdens in early life but would still be below the steady-state body burden achieved by ingestion of the TDI from birth.

Dr. G. Nordberg (Umeå, Sweden) used cadmium as an example of a contaminant where the evaluation of the significance of duration of intake above the PTWI also should be considered in relation to toxic endpoints other than that on which the PTWI had been established. The PTWI for cadmium of 500 µg, corresponding to 1 µg/kg bw/day, is based on renal dysfunction, which requires that a certain concentration be accumulated in the kidneys. Under normal dietary conditions it will take years before such levels may be achieved in the target organ. Therefore excursions above the PTWI would be of no concern provided they are followed by periods of intake below the PTWI. However, Dr. Nordberg pointed out, that cadmium could produce other effects following exposure to high intakes during shorter time periods. The LOAEL for symptoms from the gastrointestinal tract in humans after intake of a single oral dose is 43 µg/kg bw, and applying a safety factor from three to 10 produces a tolerable single dose of 4–14 µg/kg bw. For longer time exposure (months to a few years), daily intakes of 3 µg/kg bw may be tolerated without gastrointestinal symptoms. Cadmium has also produced reproductive/developmental effects in experimental animals, and although there is no convincing human evidence that 3 µg/kg bw/day can produce such effects, Dr. Nordberg found it advisable to restrict intakes to a maximum of 1 µg/kg bw/day for such potential sensitive subsections of the population as women who are pregnant or lactating and children.

DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

From the workshop discussion a number of conclusions and recommendations can be outlined to provide guidance on the assessment of the significance of excursions of intake estimated above the ADI.

General discussion

For most food additives, veterinary drug residues and pesticide residues, excursions above the ADI are probably not frequent, but they may occur more frequently for some food contaminants. It was considered that excursions above the ADI/TDI might have greater health significance for some contaminants and some pesticide and veterinary drug residues than for food additives. This conclusion was based on the greater inherent toxicity of many contaminants, pesticides, and veterinary drugs than of food additives, which are developed to be nontoxic and many of which are chemically close to normal food ingredients. Therefore, from a scientific viewpoint, the workshop conclusions are less relevant for food additives than for contaminants and residues.

Intake estimates are approximate rather than exact values, and a number of assumptions are made in the derivation of the ADI. Any numerical value derived from scientific data will be associated with some degree of uncertainty, and the precision of the estimates should not exceed the precision of the methodology. Therefore, interpretation of intake data in relation to the ADI should recognise the limitations of the estimates.

There was general agreement that the ADI/TDI and its derivation is an appropriate and scientifically credible basis for the safety assurance of food additives, pesticide residues, veterinary drug residues, and contaminants (in this case expressed as TDI) which show threshold toxicity. By experience, toxicologists have no serious health concerns about occasional excursions of intake above the ADI, provided that the intake over a longer period averages at or below the ADI, as a large margin of safety is built into its derivation. However, it was considered that excursions of intake above the ADI were generally undesirable, in particular for a prolonged period. The workshop acknowledged the common practice of regulators of taking into account maintenance of the ADI when setting maximum limits when considering high-intake consumers but no reasonable approaches can prevent extreme consumers with bizarre food habits from exceeding the ADI. In this context, identification of the level above which consumers are considered extreme is a political decision going beyond the scope of the workshop.

Despite regulatory efforts, it is not always possible to prevent the estimated intake of some substances, by some individuals, exceeding the ADI. In particular, for some ubiquitously occurring contaminants, the estimated intake might in some cases exceed the TDI or PTWI. It was therefore recognised that there is a need for more guidance and transparency for the procedures used for the derivation of the ADI/TDI and the inherent uncertainties in intake estimates. This is important because the uncertainties in intake estimates and the fact that the ADI (or even worse, the PTWI divided by seven) is not a lower bound of toxicity are not always appreciated. The derivation of the ADI is not a formal risk assessment that predicts an expected (negligible) frequency of occurrence of toxic effects at a defined exposure condition but, rather is a safety assurance procedure that defines an acceptable (lifelong) intake below which no harmful effects can be expected for the population at large.

There was also general agreement that assessments of the significance of exceeding the ADI should be performed on a case-by-case basis. The first step would be to identify compounds for which excursions of intakes above the ADI could possibly occur (occasionally or regularly) and to estimate whether any segments of the population would be at increased risk because of either high intake or increased sensitivity.

What methods should be used to estimate intakes?

Because of the complexity and expense of long-duration studies on food consumption and the associated analysis necessary for estimating food chemical intakes, it is not realistic to expect that comprehensive and precise intake data will be available for the vast majority of substances. It is therefore advised that the first step is to use a conservative, theoretical / hypothetical approach (such as the Budget Method). If no problems are encountered, there is no need for further estimation. Effort should concentrate on compounds for which a conservative estimate indicates that an excursion cannot be excluded. The next step would be a refinement of the intake estimate. The method used should take into account the specific occurrences / uses of the compound in question, and a number of issues should be considered, e.g., duration and size of study, under- and overreporting, consumers versus nonconsumers, accurate concentration data on levels in food, and portion / unit size. Of the various methods available for estimating dietary intakes, a compromise approach might be to undertake a 3-day dietary study supplemented with a food frequency questionnaire (to estimate percent of consumers). A minimum study population size would be 200 persons. If the intake estimate is still above the ADI, it would be necessary to carry out a risk assessment.

For how long can excursions above the ADI be tolerated and by how much can it be exceeded?

The likelihood of any health risk from intakes above the ADI depends on the duration and magnitude of excess intake in relation to the toxicological database, the toxicokinetics, and the pivotal study used to derive the ADI. There are no simple and standard answers, and the workshop therefore concluded that no general guidance could be given on how long and by how much excursions above the ADI could be tolerated, and that a case-by-case evaluation is required. It is essential that the whole toxicological database be consulted, in particular the findings in the pivotal study and its duration (acute, subchronic, chronic). As temporal equivalence (in a biological sense) between animal species and humans cannot be established with confidence, shorter-term studies should be used with caution if needed in the assessment.

The following typical situations may help in evaluating the significance of the duration and magnitude of exceeding the ADI:

When the ADI is based on a chronic study, an intake above the ADI should not be acceptable if it occurs throughout the major part of human life, because it reduces the overall safety margin. When the excess intake is for a period shorter than the pivotal study on which the ADI was based, consideration should be given to using a NOAEL from a study of shorter duration to determine

whether the excess intake is indeed of concern. This is because use of the NOAEL from the pivotal study (usually chronic) might under these specific conditions be too conservative and overestimate the actual risk. Importantly, the chronic study data may not be the appropriate endpoint to consider with respect to developmental stage and age at excess exposure. In such cases, there should still be an adequate safety margin between the NOAEL for the appropriate toxicity study and the magnitude of the excess intake.

For food additives and most pesticides and veterinary drugs, the half-life is normally short and toxicity may be due to chronic stress rather than cumulative toxicity. Effects on the target organ can be reversible, and short-term studies with a reversibility component may become pivotal in assessing the consequences of short-term excursions above the ADI. However, when the effects are not fully reversible, or are even progressive, the consequences of short-term peaks of intake above the ADI would require careful evaluation against the NOAEL or LOAEL in subacute or subchronic studies. A (rare) situation may arise where the ADI is based on a chronic toxicity study, but the margins between the chronic NOAEL and some aspects of acute toxicity, e.g., acute neurotoxicity or reproductive / developmental effects, may be small. In such a situation, the NOAEL from the acute study would be the appropriate endpoint on which to base the evaluation of short-term peaks of exposure and would provide the basis for deriving an acute RfD.

For a given compound, the toxicokinetic properties (such as half-life) and toxicodynamic properties (such as mode of action, including reversibility, and progression) are essential parameters to consider. The time necessary to produce toxicity depends on the presence of a "toxic" body burden and the time to achieve a steady-state body burden. For toxicodynamics it is not possible to propose general guidelines, because the situation will be specific to each chemical. For toxicokinetics there are general rules which can help predict blood levels and body burdens. During regular daily intake of a substance, the body burden will increase over a period of time until a steady state is established. At this stage the amount of substance eliminated matches the intake on a daily basis. An intake of twice the ADI will not result in a doubling in body burden unless the period of excess intake is around four to five times the half-life of the substance in question. It should, however, be remembered that not all relevant effects depend solely on average body burden over time, and a number of special situations, such as potential effects on the embryo, foetus, and breast-fed infants, may be related to peak concentrations.

The proportion of the population at possible risk of any effect depends on the magnitude of the excess intake, the margin between the NOAEL and the threshold for that effect, and variability in the kinetic parameters determining the internal dose. The severity of any adverse effect in groups at possible risk depends on the magnitude of the excess intake, the nature of the critical effect, and the slope of the dose-response curve.

Different new approaches and models (including benchmark dose, categorical regression, Bayesian approaches, and Monte Carlo models) are available or being developed for the quantitative estimation of risks (at the population or individual level) at doses above the ADI. In general the models are conservative. They are not alternatives to each other, nor are they alternatives to the ADI concept. Such approaches may give useful insight into the significance of specific exposure scenarios and contribute to our understanding of the scientific basis for the ADI and its interpretation. The usefulness of such models should be explored.

Do the same principles apply to contaminants that have TDI or PTWI values?

The derivation of TDIs or PTWIs for food contaminants is based on the same principles as the derivation of an ADI, and excursions above the TDI / PTWI should be considered in the same way as for substances where an ADI has been set.

Contaminants having very long half-lives accumulate in the body, and chronic toxicity is most often manifested when critical concentrations are achieved in target tissues. There are usually large differences between the acute or shorter-term toxic doses and the chronic LOAELs. In such cases peak excursions of several times the PTWIs for short periods (days, weeks, or even months) or lower peak intakes for even longer periods (months to years) may be of no consequence provided that the integrated exposure over longer periods does not lead to critical steady-state tissue concentrations. Consideration of interspecies differences may be complex for substances which have a half-life longer than 1 week. For example, TCDD has a half-life of 1 month in the rat but >7 years in humans. Thus, a 90-day exposure in rats would give a TCDD body burden approaching 90% of the steady state, whereas an exposure of 90 days to humans would give only 2% of the steady-state load.

CLOSING REMARKS

In her closing remarks Dr. S. Barlow summed up the view which had emerged that the average intake of food additives and contaminants should be within the ADI and that individuals should not exceed the ADI for prolonged periods. This principle applies to the population in general, and if excursions among a subset of the population are observed their relevance has to be assessed on a case-by-case basis, including consumption patterns, examinations of the toxicological database, the precision of intake estimates, and the existing regulatory framework. Dr. Barlow referred to the ADI as a beautiful woman: “Perhaps not so seductive as when she was first introduced to us by her French father, and she may need an occasional facelift. But over the years she has proved that her beauty is not just skin deep”. The workshop revealed that it is possible to look beyond the safety assurance estimate underlying the ADI concept. On a case-by-case basis that takes into account the available toxicological database including reference to toxicodynamics and toxicokinetics, scenarios where intake is above the ADI / TDI can be explored and some useful scientific tools and principles have been identified. Once information on the magnitude and duration of excursions is available, these tools may help predict the likely consequences for human health.

GLOSSARY

Absorption the process by which and the extent to which an intact compound is absorbed from the gut lumen into the portal circulation.

Acute toxicity study investigates the adverse effects occurring within a short time, usually up to 14 days, following the administration of a single dose (or multiple doses given within 24 hours) of a substance.

Acceptable daily intake (ADI) 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.

Benchmark dose the lower confidence limit of the dose calculated to be associated with a given incidence of effect estimated from all toxicity data on that effect within that study.

Biomarker any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical or biological.

'Chinese Restaurant syndrome' a collection of symptoms that some people experience after eating food served in Chinese restaurants. Syndrome is claimed to be due to monosodium glutamate but not confirmed in double-blind trials.

Chronic toxicity study a study carried out on a substance over a significant proportion of an animal's life time.

Clearance describes the efficiency of irreversible elimination of a compound from the body. Elimination in this context refers either to the excretion of the unchanged compound into urine, gut contents, expired air, sweat, etc., or to the metabolic conversion of the compound into a different chemical, predominantly in the liver, but also to some extent in other organs. When the compound has been metabolised, the parent chemical has been cleared or eliminated, even though the metabolite may still be in the body.

Critical effect the first adverse effect, or its known precursor, that occurs as the dose rate increases. There is an assumption that for some toxic responses, there is a level (threshold) below which adverse effects will not occur.

Default value pragmatic, fixed or standard value used in the absence of relevant data.

Effect a biological change in an organism, organ or tissue.

Genetic polymorphism the coexistence of more than one genetic variant in a population. It is usually related to genetic differences in activities of specific enzmes involved in toxicokinetics of xenobiotics.

Half-life the time taken for the amount of compound in the body (or the plasma concentration) to fall by half. The elimination of a compound is usually an exponential (logarithmic) process so that a constant proportion of the compound in the body is eliminated per unit time.

Lowest-observed-adverse-effect level (LOAEL) the lowest concentration or amount of a substance, found by experiment or observation, which causes an adverse alteration of morphology, functional capacity, growth, development or life span of the target organism distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Monte Carlo model a simulation model of the likelihood and the magnitude of consumers intakes of chemicals, e.g. pesticides by using continuous probability distributions of input variables, e.g. consumption of food, concentration of chemical in food etc.

Multigeneration study a toxicity test in which two to three generations of the test organism are exposed to the substance being assessed.

Non-linear kinetics describes a compound which does not obey first-order kinetics at high doses. This can arise whenever an interaction between the chemical and a body constituent is saturated by the presence of excess chemical.

No-observed-adverse-effect level (NOAEL) the greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure. Alterations of morphology, functional capacity, growth, development or life span of the target may be detected which are judged not to be adverse.

Pharmacokinetics the process of the uptake of a drug by the body, the biotransformation it undergoes, the distribution of the drug and its metabolites in the body. Both the amounts and the concentrations of the drug and its metabolites are studied.

Provisional maximum tolerable daily intake (PMTDI) an end-point used for contaminants with 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 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 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 foods.

Risk the possibility that a harmful event (death, injury, or loss) arising from exposure to a chemical or physical agent may occur under specific conditions.

Reference dose (RfD) an estimate (with uncertainty) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during lifetime. RfDs are based on non-carcinogenic effects and are usually calculated by applying uncertainty factors to the NOAEL or LOAEL. They are used by the U.S EPA.

Safety (or uncertainty) factor a factor applied to the no-observed-adverse-effect level (NOAEL) to derive an acceptable daily intake [the no-observed-effect-level is divided by the safety (or uncertainty) factor to calculate the ADI]. The safety factor is the product of several single factors. These factors account for adequacy of the pivotal study, interspecies extrapolation, inter-individual variability in humans, adequacy of the overall data base, and the nature of toxicity.

Steady-state the condition in which the amount of a compound eliminated at each dose interval equals the dose for that interval.

Subchronic toxicity study a study to demonstrate adverse effects occurring as a result of repeated daily doses of a chemical for part, commonly up to 10%, of the life-span of an animal, e.g. in rats sub-chronic studies would usually take 90 days whereas 14, 21 and 28 day studies in rats are generally referred to as ‘subacute’ tests.

Teratogenicity property (or potential) to produce structural malformations or defects in an embryo.

Threshold the dose or exposure below which an adverse effect is not expected.

Tolerable daily intake (TDI) the regulatory equivalent to the ADI applied for contaminants.

Toxic equivalent (TEQ) the contribution of a specified component (or components) to the toxicity of a mixture of related substances.

Toxicokinetics the process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the body. Both the amounts and the concentrations of the substances and their metabolites are studied. The term has essentially the same meaning as pharmacokinetics, but the latter term should be restricted to the study of pharmaceutical substances.

Toxicodynamics the process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects.

LIST OF ACRONYMS

ADI: Acceptable Daily Intake
bw: Body weight
ED: Effective Dose
EU: European Union
FFQ: Food frequency questionnaire
IPCS: International Programme on Chemical Safety
ILSI: International Life Sciences Institute
JECFA: Joint FAO/WHO Expert Committee on Food Additives
JMPR: Joint FAO/WHO Expert Meeting on Pesticide Residues
kg: kilogram
LOAEL: Lowest-Observed-Adverse-Effect Level
MSG: Monosodium glutamate
NOAEL: No-Observed-Adverse-Effect Level
PMTDI: Provisional Maximum Tolerable Daily Intake
PTWI: Provisional Tolerable Weekly Intake
RfD: Reference dose
2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TEQ: Toxic Equivalent
TDI: Tolerable Daily Intake
UF_A: Uncertainty factor (interspecies)
UF_H: Uncertainty factor (intraspecies)
µg: microgram
U.S EPA: United States Environmental Protection Agency
WHO: World Health Organization

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