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APPLICABILITY OF THE ACCEPTABLE DAILY INTAKE (ADI) TO INFANTS AND CHILDREN



CONSENSUS REPORT OF A WORKSHOP HELD IN JANUARY 1997

Organised by the ILSI Europe
Acceptable Daily Intake Task Force

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Workshop on the applicability of the ADI to infants and children: consensus report

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ILSI Europe held a 2-day workshop on the applicability of the ADI to infants and children in Genval, Belgium on 8-9 January 1997.

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ORGANISED BY THE ILSI EUROPE ACCEPTABLE DAILY INTAKE TASK FORCE

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INTRODUCTION

The use of food additives is regulated on the basis of the Acceptable Daily Intake (ADI). The enforced regulation should provide assurance that the ADI will not be exceeded when the foods are ingested by the consumer. Exposure of children to food additives has for a long time been a substantial part of the discussion on food additive safety for human health and a similar discussion has been taking place in relation to pesticide residues and contaminants in food.

Two major arguments have been used as the basis for suggestions that the use of food additives represents a higher risk for infants and children than for adults and that special ADIs should be established for this age group. One argument has been that infants and children in general are more susceptible to the effects of chemicals than adults, although this generalisation is not based on solid scientific evidence. The other relates to the fact that infants and children have a higher food intake than adults, on a per kg body weight basis. In relation to this second argument, and with respect to the European Commission requirements for information about intake of food additives, the European Union Scientific Committee for Food has recommended that intake assessment of children be considered separately from that of adults because patterns of consumption are different.

The present workshop was initiated by the ILSI Europe Acceptable Daily Intake Task Force and convened in Genval, Belgium on 8-9 January 1997 to address the applicability of the ADI to infants and children. More attention was paid to food additives than pesticide residues and contaminants in foods which were considered only briefly. A number of experts had been invited to address scientific issues in relation to the applicability of the ADI to infants and children, and from the information presented the workshop attempted to answer four specific questions:

- How big are the differences between infants or children and adults from a susceptibility point of view?
- Do testing methods cover these adequately?
- Are differences in food intake (between infants or children and adults) a point of concern?
- Are special safety factors or regulatory principles required for infants and children?

During the discussion it became evident that there was a need to agree upon the terminology to be used for the various human developmental stages and their corresponding time periods (see *Table 1*).

Table 1. Stages in human development

Developmental stage	Time period
Embryonic stage	8 days – 8 weeks of pregnancy
Foetal stage	8 weeks of pregnancy – birth
Preterm birth	24 – 38 weeks of pregnancy
Normal term birth	40 ± 2 weeks of pregnancy
Perinatal stage	29 weeks of pregnancy – 7 days after birth
Neonatal stage	birth – 28 days
Infancy	birth – 12 months (young: 0–4; older: 4–12)
Childhood	1 year – 12 years (young: 1–4; older: 4–12)
Adolescence	> 12 years – 18 years
Adulthood	> 18 years

The criterion for low birth weight (LBW) was set at less than 2 500 g (less than the 10th percentile for growth for a mature newborn; any newborn with a weight less than the 10th percentile of weight for gestational age is a small-for-gestational-age (SGA) infant). Newborns with a birth weight below 1 500 g are very-low-birth-weight-infants. In most instances they will be preterm (born before 37 complete gestational weeks) and they can be either small-for-gestational-age (SGA) or appropriate-for-gestational-age (AGA) infants.

In her opening remarks Prof. Dame Barbara Clayton, University of Southampton (UK), stressed that infants and small children are not small adults. This was illustrated by the change in total water content of the body at different developmental stages, decreasing from 94% of water in the foetus to 50–60% in an adult. The developing human is exposed *in utero* to the maternal diet, the neonate and the young infant to mother's milk, infant formulas, and weaning food, while toddlers and older children consume family food. The increases seen in recent years in atopy, asthma and food allergy are of concern as is the possibility that some effects on developmental functionality seen in adult life may be induced by exposure during childhood. In particular, it was pointed out that insufficient attention has been paid to biochemical mechanisms of metabolism in the foetal state, infancy and childhood, physiological changes occurring during development, differences in susceptibility (eg. in immunological status), and different dietary patterns.

DERIVATION OF THE ADI

Professor Ron Walker, University of Surrey (UK), explained that the widely used concept of the Acceptable Daily Intake (ADI) for humans was originally developed between 1956 and 1962 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”. This concept is now also used in the evaluation of pesticides. The closely similar Tolerable Daily (or weekly) Intake (TDI (or TWI)) is applied to contaminants in food.

Results from studies in humans, experimental animals and *in vitro* are used in deriving the ADI. The standard toxicity data set should include acute, sub-acute (28-90 days), chronic toxicity, and carcinogenicity studies. Combined chronic toxicity and carcinogenicity studies are often used in the testing of food additives. The toxicity tests also include studies on reproductive toxicity/teratogenicity covering at least exposure *in utero*, neonatally (via mothers milk) and up to weaning. In addition studies on metabolism and kinetics (preferably also in humans) as well as short-term *in vitro* studies of mutagenicity/clastogenicity are required. A number of food additives have been studied using a two generation cancer bioassay.

The reproduction studies cover the different developmental periods up to weaning, while the chronic two-year toxicity/carcinogenicity test, starting at 6-8 weeks of age in the rat, covers only part of the period of juvenile growth.

The “no observed adverse effect level” (NOAEL) is determined from the most sensitive study in the most sensitive species tested. The NOAEL is thus found by study or observation, and is the highest dose level producing no detectable adverse alterations of morphology, functional capacity, growth, development or life-span.

The ADI is established from the NOAEL by dividing it by a safety factor. When the data base is considered adequate a factor of 100 is used by default, but may be modified when adequate human data are available or based on comparative pharmacokinetic/dynamic data. In cases where the data base is defective, safety factors larger than 100 are used if it is found appropriate to establish a temporary ADI.

JECFA has made a general exception for the use of the ADI in stating that the ADI should not be considered applicable to neonates and young infants up to 12 weeks of age (WHO 1987). This threshold of exclusion has been arbitrarily and emotionally set and is not purely scientifically based. The scientific justifications are firstly, that the levels of xenobiotic-metabolising enzymes and other pathways involved in homeostasis are lower in neonates and take some time to mature, and secondly, that the protocols for toxicity testing do not mimic feeding of neonates and young infants on diets other than mothers' milk.

DIFFERENCES IN TOXICOKINETICS AND TOXICODYNAMICS BETWEEN INFANTS OR CHILDREN OR ADULTS

The safety factor of 100 has been rationalised as comprising a factor of 10 for interspecies differences (experimental animals to humans) and 10 for interindividual differences (in humans). Prof. Andrew Renwick, University of Southampton (UK), (Renwick 1993, WHO 1994) has proposed a scheme for subdividing the two components of the safety factor. In his scheme each factor of 10 has been subdivided in order to allow for differences in toxicokinetics (aspects such as absorption, distribution, and elimination which determine delivery of the chemical to its site of action/toxicity) and toxicodynamics (aspects such as target organ sensitivity, cytoprotective mechanisms, and homeostatic control which determines the extent of any effect or response due to the presence of the chemical at the site of toxicity). For differences in toxicokinetics a default factor of 4.0 was suggested for interspecies differences and of 3.2 for interindividual differences. For differences in toxicodynamics a default factor of 2.5 was suggested for interspecies differences and of 3.2 for interindividual differences. This approach facilitates an assessment of the appropriateness of the 100-fold safety factor and the applicability of the ADI to particular circumstances, such as infants and children.

Prof. Renwick examined the differences in toxicokinetics between infants or children and adults based on an extensive *in vivo* database on the pharmacokinetics of therapeutic drugs. Renal function and hepatic xenobiotic metabolism are immature in humans at birth, especially in the pre-term neonate, but mature rapidly over the first months of life. Similar changes take place in the neonatal rat during the first weeks of life, prior to weaning. He found that the elimination/clearance of the drugs examined is either similar or in many cases higher in infants or children than in adults and that this difference would apply to other xenobiotics. In consequence, infants and children frequently will have lower body burdens than adults for the same daily intake of a chemical, when expressed on a body weight basis. The safety factors available for toxicokinetic differences are adequate and the higher clearance in children would offset, at least in part, any greater target organ sensitivity.

Studies by Dr. Thierry Cresteil, National Institute of Health and Medical Research (F) using human liver microsomes have confirmed that the xenobiotic-metabolising enzymes mature rapidly during the first weeks after birth and that the liver of a three month old child has about one-third of the overall *in vitro* biotransformation capacity of the adult liver. Even the human foetal liver is active in biotransformation. The cytochrome P450 isoforms develop independently and show differences in onset.

Professor Lennart Dencker, University of Uppsala (S) stressed that *in utero* and neonatal susceptibility may depend on a number of determinants, including genotype, developmental stage, mechanism of action of the chemical, pharmacokinetics, and dose-effect and dose-response relationships. The classical malformations and/or syndromes are mainly induced during the period spanning from preimplantation through the organogenic period. In the following foetal period (after eight weeks of pregnancy) no major malformations are induced, but susceptibility to chemicals affecting specific receptors and molecular targets may have pronounced effects on a number of developmental processes. In particular, it was pointed out that the so called "brain

growth spurt” takes place during the neonatal period in experimental animals, while in humans this development begins during the third trimester. Interference with these processes may induce behavioural effects, that become manifest later in adult life. Studies in experimental animals with such chemicals as DDT, nicotine, and deltamethrin showed that neonatal days 10-14 were a sensitive window of exposure that produced behavioural effects that did not become manifest until after maturation.

Dr. Steve Olin, ILSI Risk Science Institute (USA) presented a report prepared by an ILSI Risk Science Institute Working Group, in cooperation with the United States Environmental Protection Agency (EPA) Office of Pesticide Programs on research needs on age-related differences in susceptibility to chemical toxicants. The working group was formed because there was concern at the lack of understanding of age-related differences in human susceptibility to environmental toxicants. The committee focused on three areas: cancer, immune system effects, and neurotoxicity. In each of the areas a number of specific research needs were identified.

Three examples of differences between children and adults in susceptibility to carcinogenesis were identified by the working group: ionizing radiation, ultraviolet radiation, and diethylstilbestrol (after *in utero* exposure). In animal studies, increased perinatal sensitivity has been demonstrated for a number of genotoxic, experimental carcinogens, while observations, although limited, suggest that there may not be an enhanced perinatal susceptibility for non-genotoxic carcinogens. Despite the increased perinatal sensitivity to genotoxic carcinogens, the working group was of the opinion that the standard rodent bioassays were adequate in detecting carcinogens.

Although a number of observations have revealed structural and functional differences between the immune system of children and adults and between immature and adult animals, the working group recognized that very little is known about how the developing immune system might be affected by chemicals.

The working group noted that many chemicals are known to affect the nervous system of developing animals or humans differently from that of adults. The physiological development of the nervous system is complex and takes longer than most other organ systems. There may be critical exposure periods (windows) at each stage of the development where exposure results in different effects, and there is a potential for delayed manifestation of functional effects. In addition, the timing of each developmental stage may differ across species. This makes animal-to-human extrapolation difficult. The working group was of the opinion that the current practice of using adult animals for neurotoxicity testing does not adequately address the possibility of age-related differential susceptibility to neurotoxicants. On the other hand, it was concluded that neurotoxic effects observed in animals are generally applicable as relevant indicators of a human response. Thus, it was assumed that developmental neurotoxic effects observed in animal studies indicate the potential for developmental neurotoxicity in humans.

USEFULNESS OF CURRENT TESTING PROCEDURES

Prof. Paul Peters, University of Utrecht (NL), in his talk on the adequacy of developmental toxicology also stressed that when a chemical is able to produce adverse effects in animals this indicates that it may also produce adverse effects in humans, although the specific effects seen in animals may not be assumed to be the same in humans. A list of priority factors likely to have effects on human development would include pharmaceuticals, occupational exposures, lack of specific substances in food, and alcohol. He considered food as such relatively safe. A number of recommendations were given to the investigators in the conduct, reporting and interpretation of reproductive and developmental studies. The newly formed European Teratology Information Centre was thought to be very useful for future epidemiological studies. So far, no effects have been seen related to the use of food additives, which may imply that the currently used safety factors are appropriate.

Dr. Ib Knudsen, (National Food Agency of Denmark) (DK), noted a number of biological differences between infants, children and adults. In particular, the potential susceptibility of the immature immune, reproductive, and nervous systems, as well as the possibility that interactions of chemicals with specific endocrine receptors during foetal and neonatal life may have profound effects on morphological and functional properties of these systems after maturation. Therefore, these aspects need much more attention. The present standard reproductive and developmental toxicity studies, where pups are not closely examined beyond weaning, have severe limitations in detecting developmental effects that will become manifest for the first time in the adult animal. It was again stressed that in several respects the human neonate is more developed at birth than the rat, in particular in the development of the brain.

He took the opportunity to review the general principles for the toxicological evaluation of food additives adopted by the European Commission Scientific Committee for Food (SCF) and paid particular attention to the design of the reproduction studies required. These studies should provide information on increases in sensitivity over generations, effects on the fertility of male and female animals, and effects on the embryo, the foetus, and the offspring. The design should cover at least two filial generations, and progeny should be followed through complete maturation and at least one reproductive cycle. Conventional behavioural and clinical observations are being performed in these studies and could potentially provide some information on delayed effects. However, much more attention should be given to a closer toxicological examination of the progeny after maturation. This calls for certain improvements in the current test procedures.

Dr. Knudsen found that from a research point of view the issue of sensitivity of children compared to adults has been largely ignored. On scientific grounds it was difficult to justify that infants are the most vulnerable group in the human population. Since all vulnerable sectors of the human population need protection by the ADI, precautionary principles applied in the scientific establishment of the ADI value should cover all human exposure groups. This concept is already included in the traditional safety factor approach and the default safety factor of 100 was considered adequate when proper testing had been done. Therefore, he was of the opinion that a special safety factor for infants and children is not needed. In fact, the ADI may even in some cases be over-protective.

He recognised that the ADI should not be considered applicable to infants below 12 weeks of age, since the usual toxicity test regimen does not cover this situation. This means that special considerations will have to be applied to food additives used in infant formulas intended for use as the sole nutrition for infants below the age of 12-16 weeks.

Dr. Knudsen stressed that although the views expressed were in accordance with the sentiments of the European Union Scientific Committee for Food, the Committee has not expressed its final opinion on the issue.

DIFFERENCES BETWEEN INFANTS OR CHILDREN AND ADULTS IN EXPOSURE TO FOOD ADDITIVES

Infants and children have a higher food intake than adults, on a per kg body weight basis, and they also have different dietary habits and food preferences compared with adults. This different exposure pattern to food additives needs to be kept in mind when they are used in products that are preferentially consumed by infants and children.

Dr. Knudsen cited a 1995 survey on dietary habits of the Danes which showed that, relative to their energy intake, children consume twice as much milk as adults, and that they eat more bread and cereals, fruits and sugar than adults. On the other hand they eat less cheese, vegetables, meat, fish, and eggs.

Based on comparisons of results from comprehensive British surveys of adults aged 16 to 64 years (2 197 individuals), infants aged 6 to 12 months (448 infants), and young children aged 1.5 to 4.5 years (1 675 children), Dr. Sandie Lawrie, Ministry of Agriculture, Fisheries and Food (UK), concluded that, on a body weight basis, energy requirements, protein requirements and water intake may be up to 3, 2.5, and 5 times higher, respectively, for infants and young children than for adults. The average consumption of the main food groups, such as fruit and vegetables, bread and cereals, meat, fish and eggs, dairy products, and sugar and confectionery was found to be about 2.5 times higher in young children than in adults. In this age group, the average consumption of non-alcoholic beverages was about 2 times higher, however the consumption of preferred beverages such as soft drinks was more than 10 times higher.

An example was provided by United Kingdom data showing that a group of young children consuming a high amount of soft drinks (97.5 percentile; more than 1 litre per day), would ingest 6.4 mg of saccharin per kg of body weight per day, which exceeds the ADI of 5 mg per kg of body weight. For the great majority of young children the ADI would not be exceeded, but caution should always be exerted when setting limits for the use of food additives in these types of foods and beverages. This finding resulted in revised advice on the dilution of juice concentrates (squashes) which were the main source of intake.

INFANT/CHILD-SPECIFIC CRITERIA FOR PESTICIDES

Dr. Anthony Huggett, Nestlé Research Centre (CH), discussed the applicability of the ADI to infants and children with regards to pesticides and presented recently proposed infant/child-specific safety criteria which may be used as the basis to establish regulatory limits for pesticide residues in baby foods.

Particular attention was paid to delayed post-natal toxicity. This effect has been observed for several neurotoxic pesticides in adult animals, as a result of exposure to subtoxic doses of pesticides during a developmental period of high susceptibility. Potential functional toxicity was not thought to be restricted to the central nervous system, but may be applicable to any organ system that undergoes critical developmental processes during the period of exposure. Concern was also expressed for delayed effects on the reproductive and immune systems.

In contrast to food additives, neuro-, endocrine- and immuno-toxicity are frequently observed with pesticides, and this raises the question whether the current toxicological database for pesticides is sufficient to fully assess potential developmental adverse effects. This may not always be the case. For instance, impairment of the central nervous system, leading to behavioural, memory and learning deficits is difficult to identify in conventional studies. Delayed toxicity resulting from exposure to low levels of a toxicant during a particularly sensitive developmental period may not always be adequately addressed by current testing procedures.

A decision tree was presented for the derivation of the ADI which also ensures adequate protection for infants against pesticides. The scheme takes into account the potential for delayed functional toxicity, when all endpoints are not covered in the toxicological data. Where adequate reproductive and teratogenicity testing has not revealed adverse effects at a dose level that produces mild adult toxicity, and in addition, if there is no indication of potential post-natal functional toxicity in the overall database, the pesticide probably does not carry a particular risk for developmental toxicity and therefore the current ADI is appropriate. However, if information indicates a potential post-natal functional impairment (such as neurotoxicity in the adult), the toxicological database should be considered inadequate in the absence of proper developmental studies addressing this issue. In that case a larger safety factor is warranted, its size being dependent on a case by case evaluation.

DISCUSSION AND CONCLUSIONS

Based on the presentations and discussions the workshop addressed the questions put forward at the opening of the meeting.

How big are the differences between infants or children and adults from a susceptibility point of view?

Based on the existing knowledge, this question cannot be given a simple and general answer and no numerical figures can be established that reflect differences in susceptibility between infants or children and adults. Differences in susceptibility are a function of toxicokinetic and toxicodynamic parameters, including genetic, physiological, and metabolic factors, mechanism of action of the chemical and dose-effect and dose-response relationships. Special concerns for infants and children relate to the developmental state of their biochemical and physiological processes.

In order to address the differences in susceptibility, an inverse approach examining the adequacy of the safety factor was used. According to the original premises defined by JECFA and European Commission Scientific Committee for Food, the appropriately sized safety factor is supposed to cover differences in species sensitivity, synergistic or antagonistic actions among food additives and other components of food, the heterogeneity of the exposed human population with regard to pregnancy, physiological status and nutrition, age differences between exposed individuals and the variability in susceptibility with age to the potential adverse effects of an ingested toxic substance.

The default safety factor of 100 has later been rationalised as comprising a factor of 10 for interspecies differences (most sensitive experimental animal species to humans) and 10 for interindividual differences in humans. The two components of the safety factor were suggested to be subdivided in such a way that each factor of 10 allows for differences in toxicokinetics and toxicodynamics. From examination of the differences in toxicokinetics between infants or children and adults it has been found that the elimination/clearance of xenobiotics is either similar to or in many cases higher in children than in adults. In consequence, children frequently will have lower body burdens than adults for the same daily intake of a chemical, when expressed on a body weight basis. Based on this, it was concluded that an increased safety factor was not required for differences in toxicokinetics between post-suckling infants or children and adults. In addition, it was speculated that the higher clearance of many xenobiotics by children may compensate for eventually increased organ sensitivity during development and growth.

The workshop emphasized that this conclusion does not apply to infants before the age of 12 weeks during which period the maturation of the xenobiotic metabolising systems and elimination processes take place. In fact, these processes may have a significantly lower capacity in pre-term infants.

Toxicokinetics is only a part of each safety factor of 10. A systematic review has not been performed on differences in toxicodynamics. Nevertheless, experiences gained from toxicological studies in experimental animals strongly suggest that it is not possible to make general statements about age-related differences in toxicodynamics. For some chemicals, immature animals are more sensitive than adults while in other cases they are less sensitive, depending on the compound and its effects. In humans, the same picture emerges from experimental and clinical data on pharmaceuticals, while knowledge about age-related differences in susceptibility to food additives is virtually absent.

Particular concern was expressed as regards the susceptibility of the developing foetus, neonate, infant and child to delayed functional toxicity becoming manifest in adult life, as a result of

exposure to apparently subtoxic doses of toxicants during a developmental period of high susceptibility. Developmental functional toxicity may be particularly relevant for the developing central nervous system, but will also apply to other systems, such as the endocrine, reproductive, and immune systems. However, it was stressed that the database was insufficient to allow any meaningful general conclusion about the potential for delayed toxicity from exposure to chemical substances during the foetal/neonatal periods. Moreover, the opinion of the workshop was that such effects were less likely to occur with food additives than with pesticides.

Overall, the workshop concluded that the issue of age-related differences in susceptibility to food additives and other compounds should be addressed on a case by case basis.

Do testing methods adequately cover age-related differences in susceptibility?

As a result of the examination of age-related differences in toxicokinetics it was concluded that no major systematic differences between neonatal and young animals and their human counterparts were seen for several toxicokinetic parameters, and that an increased safety factor is not required for interspecies differences provided that the toxicodynamic endpoints have been adequately studied and considered carefully.

As the xenobiotic-metabolising enzymes are somewhat more developed in the human foetus and neonate than in the foetal and neonatal rat, it has been argued that experimental animals would be more sensitive to the toxicity of many chemicals than would humans, and that this might provide an extra margin of safety. This argument would not hold true for chemicals that require metabolic activation in order to exert toxicity, such as many genotoxic carcinogens. However, such compounds are of no practical relevance for food additive use.

Among the traditional toxicological methods used in food additive safety testing, the reproduction studies cover different developmental periods up to weaning, while the usual chronic two-year toxicity/carcinogenicity tests, starting at 6-8 weeks of age in the rat, cover only the late period of juvenile growth. The ADI derived from these studies is thus intended to cover exposure of older infants and children as well as exposure of the foetus during pregnancy and the neonatal and young infant during the nursing period.

Concern has been expressed as to whether the currently used test methods adequately cover the potential susceptibility (in a highly sensitive exposure window) of the developing foetus, neonate, infant and child to delayed functional toxicity that first becomes manifest in adult life. Although it was noted that the clinical examinations performed in the currently used toxicity tests, including multigeneration studies, may reveal obvious signs of functional deficits, the workshop agreed that this aspect deserves more attention in the future. In the light of the present knowledge, the standard test package ought to be refined in both design of studies and the choice of parameters examined. More attention should be given to parameters that adequately address the function of the nervous, reproductive, endocrine, and immune systems. It was recommended that in order to fulfil this goal more research into refined, but feasible, parameters should be initiated. The workshop also expressed the need for a careful consideration on how differences between humans and experimental animals in the timing of particular stages in the development of different organs will affect the design of test procedures and evaluation of test results. As an example, in the development of the central nervous system the "brain growth spurt" starts in the third trimester of human pregnancy and may be adversely affected following transplacental passage of a toxicant ingested by the mother, while in the rat this process takes place in the neonatal period where exposure to the toxicant requires that it is excreted in the mother's milk.

A two-generation protocol, in which the F1-generation is used for the evaluation of chronic toxicity would cover exposure *in utero* and throughout the suckling period including "creep

feeding” (consumption of adult diet during suckling) preceding complete weaning, as well as the rapid juvenile growth phase immediately post-weaning. This model was advocated by several participants, especially if adequate parameters to examine delayed functional toxicity were included.

The usual toxicological test battery does not mimic the human situation with ingestion of infant formula, and therefore the workshop did not consider the ADI applicable to infants below 12 weeks of age. Therefore, the use of food additives in infant formula, if necessary, will require special testing and evaluation on a case by case basis.

In practice some parents (in spite of advice) give their pre-weaning babies weaning food or family food potentially containing food additives in addition to mother's milk or infant formula. However, the workshop did not consider this to be a problem in most situations as only small amounts would be given to pre-weaning babies. This situation could be seen as a parallel to “creep feeding” in experimental animals. In any case regulators cannot regulate such behaviour of parents, only issue recommendations.

Are differences in food intake (between infants or children and adults) a point of concern?

Infants and children, on a per kg of body weight basis, eat more food and drink more milk and non-alcoholic beverages than adults. They also have other dietary habits and food preferences different from those of adults. This means that infants and children potentially will have a high daily intake of those food additives which are used in the types of foods and drinks they consume and prefer. This should concern the regulator and be taken into careful consideration when the ADI is used to establish the use levels of food additives in such foods. The fact that infants and children have a higher intake of some food items than adults is not part of the ADI, and should clearly be considered in the risk management.

Some argued that this higher dietary intake of food additives by infants and children was to some extent reflected in those toxicological studies (mainly of an older date) where the additive had been incorporated at a fixed concentration in the feed of the animals and where the studies had started at 6-8 weeks of age in the rat. However, this higher intake in the young animals of the test compound has never been taken into account in the derivation of the ADI. Moreover, it was argued by several participants that this design was not particularly useful and should be avoided in toxicological studies due to the interferences that possible nutritional imbalances might create.

Are special safety factors or regulatory principles required for infants and children?

The workshop strongly recommended that special safety factors for infants and children should not be used, and consequently special ADIs should not be established. The toxicological database should adequately cover the most sensitive effects and the most sensitive age groups. The overall ADI should cover all sensitive segments of the population, irrespective of age.

If there is scientific evidence that infants and children are most sensitive to a particular food additive, that evidence must influence the derivation of the ADI. Regulatory questions thereafter relate to the probability of exceeding the ADI.

It was thus the opinion of the workshop that the most sensitive endpoint of toxicity in the test data should influence the ADI determination. Larger safety factors than usual should be reserved for use when the toxicological database was considered inadequate according to the state of the art in food toxicology. The workshop also stressed the need for reevaluating food additives within a certain time frame in the light of new data created by up-to-date methodology.

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