

Opinion of the Scientific Committee on Food on the applicability of the ADI (Acceptable Daily Intake) for food additives to infants (expressed on 17/09/1998)

1. Terms of reference

To consider the applicability of the ADI (Acceptable Daily Intake) for food additives intended for use in foods for infants in the age of 0-16 weeks.

2. Background

The 1st meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) held in Rome in December 1956 introduced the term *Acceptable Daily Intakes*, ADI, as a tool for the safe use of food additives. The ADI describes the daily amount of a compound that an individual can be exposed to throughout life without adverse effects. This concept has now been introduced in food regulation world wide to ensure that the ADI will not be exceeded during expected food intake by the consumer. The introduction of this concept has also guided the toxicological testing of food additives before they are accepted in the food supply (SCF, 1980; JECFA, 1987). The ongoing discussion about the predictivity and sensitivity of the introduced testing methods, especially with regard to the most vulnerable segments of the human population such as young, old, immunosuppressed and pregnant leads to continuous optimisation of the test guidelines. Presently the question has been raised whether infants in the age of 0-16 weeks are more susceptible to chemical insults than older children and adults. At its 1971 meeting, JECFA expressed the opinion that children should not be exposed to food additives before the age of 12 weeks, and that the ADI does not apply to children below the age of 12 weeks (WHO, 1978). The scientific support for that opinion is not presented in any details in the report.

The SCF in its First Report on the Essential Requirements of Infant Formulae and Follow-up Milks Based on Cows' Milk Proteins (Opinion expressed 27 April 1983) endorsed the principle that technological additives should not be used in food for infants and young children. Although the amount of additives in these foods should be limited as far as possible, the SCF did recognise that technological additives may contribute to the total nutrient content and did acknowledge that the manufactures do require a certain amount of choice to meet both objectives. "For this reason the list of additives is somewhat longer than at first sight might seem compatible with the principles of non-use of additives in food for this age group" (Comm. of EU, 1983).

In its "Opinion on Certain Additives for Use in Infant Formulae, Follow-on Formulae and Weaning Foods" expressed 11 December 1992 the SCF reiterates its view that consideration of the safety of additives for use in infant formulae, follow-on formulae and weaning foods is a special case. The immaturity of the organs of absorption, metabolism or excretion may mean that the distribution of an additive in the body is different in the infant and young child than in the adult. In addition, developing organs and tissues may show greater sensitivity to the effects of an additive than mature organs and tissues. The SCF noted that infant formulae milks can constitute virtually the entire infant diet and therefore patterns of exposure to additives used in such formulae is very different to the normal situation of additives approved for general food use. For all these reasons the SCF considered it prudent that the number and amounts of additives used in foods for infants and young children should be kept at the minimum necessary. The SCF confirmed its long standing view that additives should not be permitted in foods specially prepared for infants. Rarely, exceptional technological circumstances may justify the use of an additive. In such cases submissions should be accompanied by a full justification for the use requested (Comm. of EU, 1994). One further food additive was accepted for infant formulae, two for follow-on formulae and one for weaning foods. In 1996 the SCF adopted an opinion on additives in nutrient preparations for use in infant formulae, follow-on formulae and weaning foods based upon further information about the functions of and justification for the use of these additives as well as quantitative estimates of levels of carry-over in the final food (Comm. of EU, 1997). Carry-overs were accepted for 13 food additives in infant formulae, follow-on formulae and weaning foods

3. Biological differences between infants on the one side and children and adults on the other which may increase susceptibility of infants to chemical insults compared to other segments of the population.

No systematic research has been performed to address this issue, but information to assess this question is scattered throughout the scientific literature.

Basically infants are in a progressive stage of development and growth. Infants do have a higher metabolic rate than children and adults. The relative weight gain during the first 6 months of life is higher than during any other period in life. In consequence, the oxygen consumption and the requirement for energy and fluid is greater in infants than in children and adults (Plunkett et al. in Guzelian et al., 1992).

In the new born infant, gastric pH is relatively high and only reaches acidity at several months of age. This means that the ionisation state of chemicals in the gastrointestinal tract and consequently the possibility for passage of chemicals into the body will be different in the infant compared with older children.

Protein binding in the newborn is low, which means that the amount of free chemical which is the active form could be greater (Snodgrass in Guzelian et al. 1992). The volume of distribution for the chemical in a premature infant may be twice as large as than of an adult. The newborn infant has a high water content, which may reach 85 per cent in the premature infant, against 50 per cent in the adult (Plunkett et al., in Guzelian et al. 1992).

The infant only reaches adult levels of most enzyme systems by 2-3 months of age. A low capacity to metabolise xenobiotics may thus make the infant less able to detoxify chemicals and consequently more susceptible to toxicants. However, the metabolites of the chemicals may sometimes be more toxic than the parent compounds and in such cases the low metabolic capacity may actually protect the infant against toxicity, e.g. acetaminophen hepatotoxicity (Kaufmann, 1992).

The renal excretion depends on the maturation of the kidney. The glomerular filtration is slow in new-born infants (30-40 per cent of adult values) but increases to adult value by 1/2-1 year of age. Tubular secretion is also lower in infants than in adults. This is counteracted by the low ability to concentrate urine which only reaches adult value at 16 months.

Certain drug receptors are not developed in the infant and chemicals may produce opposite effects in infants and adults, e.g. phenobarbital (Kacew, 1992).

Epidemiological data show that the development of allergy from oral sensitisation apparently occurs only within the first year of life. The special sensitivity of infants may be related both to an increased uptake of allergens, and immaturity of the local and systemic immunological responses. The mechanism is not fully understood (Vos et al., 1996). Since several components of the immune system are not fully developed at birth it is possible that chemicals may interfere with the development of this system (Schilter et al., 1996).

During early development substances with hormone like effects may have profound effects in both sexes (Chapin et al, 1996; Toppari et al, 1996).

Brain weight at birth is about one third of adult weight, and 75 per cent after two years. The blood brain barrier is not complete until around 6 months after birth. The development of the brain takes place over a much longer time span than other organs. Cell migration to the cerebral cortex, hippocampus and cerebellum is not completed until several months after birth. Because of the very long and complex developmental phase of the brain, and the very grave consequences for the individual with impaired brain function, it is important that the unharmed development of this organ receives great attention.

Differences in toxicokinetics between infants and children and adults have been studied in an extensive database on the *in vivo* pharmacokinetics of therapeutic drugs (Renwick, 1997). From this database it is concluded that the

elimination/clearance of the drugs examined is either similar to or in many cases higher in infants (or children) compared to adults and that this difference would apply to other xenobiotics.

Thus the most important biological differences between infants and children/adults do not relate in general to the toxicokinetics of xenobiotics, but to the toxicodynamics of these compounds especially because of the immaturity of the cells and tissues and their rapid growth in infants.

4. Relevance of the toxicity data package presently required by the SCF for food additives, to the exposure situation of infants.

The SCF has listed its requirement for toxicity data for food additives in its report on guidelines for the safety assessment of food additives expressed 22 February 1980 (Comm. of EU, 1980). In this report SCF also explained its principles for performing the safety assessment leading to the ADI. The *no-observed-adverse-effect-level* (the NOAEL) in the most sensitive experiment among the studies performed with the test compound is identified and this value is divided with 100 to establish the *acceptable daily intake* (the ADI) expressed in mg per kg body weight per day, which may be ingested over lifetime. The SCF does underline that the establishment of the ADI is not a mechanical procedure but the result of a thorough *case-by-case* procedure taking into account the biological properties of the individual food additive. This includes the possibility that the biologically most sensitive period for a compound is only a very short period in a certain phase of the life of the individual, and that the ADI derived in this case therefore may be over-protective for the majority of the population.

The mammalian guideline studies for chronic toxicity and carcinogenicity allow detection of effects in animals being exposed soon after weaning. In standard reproductive toxicity and developmental toxicity studies, animals are exposed *in utero* and during lactation, reflecting the human situation. Since the structure of the placenta and the rate of foetal and perinatal development differ between species, these differences impose the need for the use of the traditional safety factor accounting for species differences.

However, if a food additive is intended to be used in food for infants below the age of 16 weeks a special evaluation need to be performed, since this type of exposure is not covered by the usual animal studies listed above. These studies do only cover the intake through regular food or through the mother's milk until weaning. None of the studies usually recommended by SCF or JECFA to assess food additives have intended to mimic an exposure situation similar to the situation where an infant is fed totally on infant formula.

Therefore special studies in man or animals are recommended in order to investigate the possible adverse effects of the direct oral exposure of the food additives from infant formulae to infants below 16 weeks. Since the new-born rat is not developmentally parallel to the new-born human e.g. in regard to brain development (Ostergaard et al 1998), the studies must be designed and interpreted with this knowledge in mind. Other animal models should be considered. One model might be chronic studies starting in new-born piglets raised solely on mother's milk replacement, where the additive in question is added at different dosage levels.

5. Conclusions and recommendations

Infants may respond differently from adults to chemical insults, because they are in a very progressive state of growth and development; or because of differences in toxicodynamics or occasionally in toxicokinetics; or because of differences in intake.

Presently available data are mostly addressing toxicity and therapeutic effects of pharmaceuticals, while the effects in infants of other chemicals, including food additives, are less well documented. Nevertheless these data indicate great similarities in the overall outcome of the uptake/excretion processes in infants and children/adults, while the potential for specific toxic effects in the different tissues are highly influenced by the faster growth and development of the different cells and tissues in the infants compared to older children and adults. The potential for cellular toxicity in infants needs to be assessed on a case-by-case basis, because toxic effects on early cell stages and heavily dividing cells

during infancy may have different and more severe effects on the individual later in life than toxic effects on mature cells in the same individual imposed during adulthood when the cells are not developing, growing and dividing to the same extent.

The toxicological data required for food additives and used as the basis for establishing the ADIs covers adequately exposure during all life stages including special emphasis on reproductive cells, on the foetus and on the young and old organism (Comm. of EU, 1980). However, the specific exposure situation with direct exposure of infants to food additives due to the use in infant formulae intended for use as the sole nutrition for infants below the age of 16 weeks is not included in the standard toxicity test protocols. Therefore a special evaluation beyond the present ADI evaluation is needed before food additives are to be accepted for use in infant formulae for infants in the age 0-16 weeks.

6. Literature

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