Opinion of the Scientific Committee for Food on: A maximum residue limit (MRL) of 0.01 mg/kg for pesticides in foods intended for infants and young children (expressed on the 19th September 1997)

Terms of reference

The Committee is asked to advise the Commission as to whether a maximum residue limit (MRL) of 0.01 mg/kg for pesticides in manufactured foods intended for infants and young children (dietetic foods) would be adequate to protect the health of this section of the population or whether there are instances where there are reasons to be concerned that the presence of even lower levels might constitute a risk. In the latter case, the Committee is invited to provide criteria for the identification of the pesticide residues concerned and for the establishment of appropriate residue limits for them.

Background

In its opinion on the essential requirements for weaning foods (European Commission 1990), the Committee defined "Infants" as children aged less than 1 year and "Young children" as children aged between 1 and 3 years. For the purposes of the present opinion," older infants" are those aged between 4-12 months and "childhood" is understood as the period from 1 year to 12 years (young child 1-3, older child 3-12 years).

Foods for particular nutritional uses (dietetic foods) intended for infants and young children are covered by two directives: Directive 91/321/EEC (EEC,1991a)as amended by directive 96/4/EC (EEC, 1996a) on infant formulae and follow-on formulae and Directive 96/5/EC (EEC, 1996b) on processed cereal-based foods and baby foods. Article 6 of each of these directives specifies that the products covered "shall not contain any substance in such a quantity as to endanger the health of infants and young children. Necessary maximum levels shall be established without delay".

The terms used in these Directives are consistent with those defined by the Committee.

Pesticide residues are regulated by Directives 76/895/EEC (EEC 1976), 86/362/EEC (EEC 1986a), 86/363/EEC (EEC 1986b) and 90/642/EEC (EEC 1990) and their amendments. These directives do not harmonise the situation for foods intended for infants and young children, however, the Commission declared to the Council during the adoption of these Directives its intention to present proposals for maximum levels of pesticides in foods intended for infants and young children by 1 January1999.

Taking account of the various scientific, practical and socio-economic factors, the Commission has asked the Committee to advise it on the health implications of a limit of 0.01 mg/kg for pesticides in manufactured foods intended for infants and young children in the light of current scientific knowledge.

Current procedures for establishing maximum residue revels (MRLs) for pesticides

The use of pesticides is regulated on the basis of the MRLs established for residues on various crops. The establishment of a MRL should, among other things, take into account that the Acceptable Daily Intake (ADI) for humans for that particular pesticide is not exceeded when the foods are ingested by the consumer. The ADI is defined as "an estimate of the amount of a residue, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk" (WHO, 1987). The ADI is intended to cover all vulnerable groups (including different age groups) within the human population. It has been stated that the ADI is applicable to children older than 12 week of age. (FAO/WHO,1978). JMPR (Joint FAO/WHO Meeting on Pesticide Residues) has been establishing ADIs since the early 1960s.

MRLs are subsequently derived based on GAP (1) supervised trials and compared with the ADI. In the EC there is a tiered approach in the setting of the MRLs (Directives 86/362, 86/363, 90/642 and 91/414 (EEC 1991b)). Firstly, the TMDI (theoretical maximum daily intake) is calculated from the MRL proposals based on the results of the GAP supervised trials and the estimated food consumption per person. If the ADI is exceeded according to this calculation, more refined methods are used to calculate a more realistic intake using e.g. the actual median residue levels determined after GAP supervised trials, and reduction factors from the processing of food. If the ADI is still exceeded after use of the refined calculation methods, then the proposed MRLs cannot be endorsed.

(1) Good Agricultural Practice in the use of pesticide includes the nationally authorized safe uses of pesticides under actual conditions necessary for effective and reliable pest control. It encompasses a range of levels of pesticide applications up to the highest authorized use, applied in a manner which leaves a residue which is the smallest amount practicable. (Codex alimentaruis commission, CL 1996/33 - PR, p.17)

Differences in susceptibility between infants, children, and adults

In contrast to adults, children, and in particular infants are in a progressive stage of development and growth. Potential differences in susceptibility to pesticides are dependent on toxico-kinetic and toxico-dynamic parameters (such as organ sensitivities), 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 early developmental state of their biochemical and physiological processes. Therefore it needs to be considered whether exposure of these age groups to pesticides may lead to more serious toxicological effects or even effects not induced in the adult.

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 pesticides during a developmental period of high susceptibility (critical window) is of particular concern. Developmental functional toxicity may be particularly relevant for the developing central nervous system, but also applies to other systems, such as the endocrine, reproductive (e.g. reduced semen quality due to impairment of Sertoli cell development), and immune systems. Although delayed neuro-toxicity has been observed in experimental animals after exposure to some pesticides, the current databases do not allow any unified conclusions about the potential for delayed toxicity in humans from exposure to pesticides.

The overall experience gained from toxicological studies in experimental animals strongly suggest that it is not possible to make general statements about age-related differences in toxico-dynamic parameters, such as organ sensitivity. 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 pesticides is virtually absent. Therefore, the issue of age-related differences in susceptibility to pesticides should be addressed on a case by case basis.

Adequacy of current animal testing protocols for the risk assessment of pesticide residues in the diet of infants and young children

The reproduction studies cover different developmental periods up to weaning, and in the case of multi-generation studies from conception to adulthood, 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 neonate and young infant during the nursing period.

An examination of age-related differences in toxico-kinetics has shown that there are no major systematic differences between neonatal and young animals and their human counterparts for several toxico-kinetic parameters, and that an increased uncertainty factor is not required for inter-species differences provided that the toxico-dynamic endpoints have been adequately studied and considered carefully.

In several respects, the human neonate is more developed at birth than the neonatal rat. For instance, the major growth of the brain takes place before birth in humans while this occurs after birth in the rat. During lactation, the human infant will therefore probably not be as vulnerable as the neonatal rat toward effects on the development of the central nervous system. Therefore, the new born rat is not developmentally parallel to the new-born human, and studies using new born pigs or monkeys may provide better models for the exposure situation for young human infants.

Carcinogens will generally be detected in regular carcinogenicity studies. The U.S. EPA has made a comparison of carcinogenicity studies with perinatal and adult exposure, and adult exposure only (EPA, 1997). They found that the incidence of tumours may increase, and the latency period may be reduced in studies with combined perinatal and adult exposure compared to adult exposure only. Perinatal exposure though, rarely identifies carcinogens that are not found in standard carcinogenicity studies.

An area of particular concern is the possibility that interactions of chemicals with specific endocrine receptors during foetal life and infancy may have profound effects on morphological and functional properties of these systems after maturation. 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, as for instance impairment of the central nervous system, leading to behavioural, memory and learning deficits are rarely examined in

conventional studies, and 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.

At present, no single test approach for developmental behavioural toxicity has been identified as the most appropriate.

Although the clinical examinations performed in the currently used toxicity tests, including multi-generation studies, may reveal obvious signs of functional deficits, this aspect deserves more attention in the future. It would be expected, that many, but not all substances having a toxic effect in the nervous system of the new born, would show some effect in the adult at least at higher doses. 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. A new guideline regarding developmental neuro-toxicity is being prepared within the OECD test guideline programme in order to obtain more information about these effects.

None of the present standard toxicological tests mimic the situation where a human infant is exposed to chemicals via infant formulae. Therefore special considerations are needed for pesticides likely to be found in infant formulas for infants below the age of 16 weeks.

Exposure of infants and young children to pesticides from commercial infant formulae, cereals and other weaning foods

Infants and young children have a higher food intake than adults when expressed on a per kg body weight basis. The dietary exposure of infants in their first few months of life to pesticides arise primarily from breast-feeding (human milk), infant formulae, and water. From the age of about 4 months, infants are exposed to pesticides through consumption of manufactured foods including infant formulae, follow on formulae and weaning foods and also from ‘ family food’ and drinking water used to reconstitute dry products.

Infant formulae can be divided into "ready to feed" products and those consisting of dry powder for mixing with water immediately before use. Water is the major ingredient in infant formula and the water used for the "ready to feed" formulations during manufacturing is understood to be purified by for example active carbon filtration and is thus anticipated not to contain pesticide residues of concern. Tap water is most commonly used to reconstitute infant formula in the home although bottled and natural mineral water may also be used. In this risk assessment, the Committee has taken note of the current and proposed EU limits for pesticides in drinking water (EEC 1990,European Commission 1994) which are 0.1 µg/l for individual substances and 0.5 µg/l for the total pesticide content. The Committee estimated that the contribution to the overall pesticide content arising from the use of drinking water containing pesticides at these maximum permissible levels to reconstitute dry products would be one or two orders of magnitude lower than that which could result from the products themselves if they contained pesticides at the MRL of 0.01 mg/kg.

The solid fraction of liquid infant formula typically constitutes about 13 % of the finished product. The main part is processed cows milk or soy products and corn syrup. All raw materials used have been processed which should reduce the pesticide content. It has been stated that, in general, none or very small amounts of pesticides are found in infant formulas (NRS, 1993).

The estimation of the potential exposure from manufacured food was made by adopting a worst case approach i.e. assuming that these foods constitute the total diet of a reference child. The calculation uses the physiological requirements of infants at various ages for energy and macronutrients to determine the amount of "solid matter" being consumed daily in fomulas and weaning foods. As they mature, infants consume smaller volumes of formulas as their intake of weaning foods increases. i.e. the energy density of their diet increases and the hydration factor for the solids consumes falls. On this basis a worst case scenario for exposure to solids can be hypothesised for 12 month old infants. For such infants, using a hydration factor of 33 % and an energy requirement of 1000 kcal/d, an energy density of 3 kcal/g can be derived which in turn gives an intake of 30g/kg body weight per day for a 10 kg infant. By applying two standard deviations (the standard deviation from the literature for these data is 30 %) to this mean, the value of 48 g/ kg/d is obtained.

The Committee had the opportunity to test this approach by comparing this calculated value with an estimate made from the the results of the DONALD study (Forschungsinstitut fur Kindernahrung, Dortmund) which employs consecutive three-day weighed diet records to study the food consumption patterns of infants and young persons in families from favourable social backgrounds in the Dortmund area of Germany. The study provided data for the consumption of manufactured infant formulae (dry), cereals and milk cereals (dry), and other weaning foods (ready-to-eat) as sold.

The data from the DONALD study were used to generate a frequency distribution for the total daily consumption of manufactured infant formulae (dry), cereals and milk cereals (dry), and other weaning foods (ready-to-eat) as sold based on the individual dietary records of children in each age category.

The 95 % iles of consumption estimated from the DONALD study were judged to be consistant with the value of 48g/kg body weight as calculated above on the basis of energy requirements. A worst case intake estimate was made by assuming this level of daily consumption for all infants and young children and that all the commercial products consumed were appropriately hydrated and contained a pesticide residue at 0.01 mg/kg. This would lead to a maximum estimated intake of a pesticide of about 0.0005 mg/kg b.w./day. On the other hand, if the infant’ s intake were derived from a commercial/manufactured dry product which was reconstituted as recommended (customarily 2 parts dry food product to 1 part water), the resultant exposure from a residue of 0.01 mg/kg would be 0.0003 mg/kg.b.w./day.

Conclusions

The Committee is asked to advise the Commission as to whether a maximum residue limit (MRL) of 0.01 mg/kg for pesticides in manufactured foods intended for infants and young children (dietetic foods) would be adequate to protect the health of this section of the population or whether there are instances where there are reasons to be concerned that the presence of even lower levels might constitute a risk. It concludes as follows:

The ADI covers all groups of the population. The Committee does not recommend the use of special uncertainty factors for infants and children or the establishment of special ADIs for this age group. The toxicological database should adequately cover the most sensitive effects and the most sensitive age groups and the ADI should cover all sensitive segments of the population, irrespective of age. If there is scientific evidence that infants and children are the most sensitive populations to a particular pesticide, that evidence must drive the derivation of the ADI.

The Committee recognised that the currently used data package for the establishment of the ADI was not in all respects optimal to reflect a particular sensitivity of infants towards the potential toxicity of a given pesticide. However, it was the opinion that in most cases the toxicological studies would have provided indications if such special sensitivities were to exist. The Committee concluded that the current ADIs would provide a reasonable basis for evaluating the health impact of pesticides in foods intended for infants and young children.

The fact that infants and children have a relatively higher intake of some food items than adults should clearly be considered in the risk assessment. This is not always taken into consideration when setting MRLs.

The Committee considered 0.0005 mg/kg b.w to be a realistic worst case estimate for the upper limit for the daily intake of a pesticide arising from the consumption of manufactured infant formulae (dry), cereals and milk cereals (dry), and other ready-to-eat weaning foods . The estimate assumes that all infants and young children consume commercial products at the highest recorded 95 percentile every day and that all commercial products contain the pesticide at a level of 0.01 mg/kg in the products as sold.

The Committee concluded that if the maximum residue limit were to be set at 0.01 mg/kg in foods intended for infants and young children, there is a possibility that an infant could exceed the ADI for pesticides having an ADI at 0.0005 mg/kg b.w. or lower

This would imply that the Commission and the Member States should carefully reconsider pesticides that have been allocated ADIs at 0.0005 mg/kg b.w. or lower as to the health impact of their presence in baby food. This consideration should include an examination of their actual use and the basis on which the ADIs was set, i.e. whether the toxicological data package gives any reason for special concerns for infants and children.

The Committee was also aware that some pesticides share a common mechanism for their critical toxic effect which determined the ADI, but do not necessarily share a group ADI. The Committee recommends that further consideration be given by the appropriate bodies to the potential for additive effects and whether the risk management of residues in foods specially manufactured for infants and young children needs to take these into account.

In giving its opinion, the Committee wishes to note that the limit of 0.01 mg/kg has not been proposed on the basis of toxicological evaluation. Therefore, for those pesticides having an ADI greater than 0.0005 mg/kg b.w., their presence in foods intended for infants and young children at levels exceeding 0.01 mg/kg does not necessarily imply a risk to their health.

When setting MRLs for pesticides in foods intended for infants and young children, the Committee draws attention to limitations of current routine analytical methods for determination of some pesticides particularly at levels around than 0.01 mg/kg.

The Committee notes that pesticide are subject to continuous re-evaluation within the EC and elsewhere, and recommends that special attention is paid to the potential higher susceptibility of infants and children to certain compounds during this process. This will require further research which may lead to improved test strategies.

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