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RISK ANALYSIS IN RELATION TO EXPOSURE OF CHILDREN TO PESTICIDE RESIDUES

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ABSTRACT

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A short literature review was performed regarding the (potential) effects of pesticide residues on children. The conclusion of the (mostly American) literature, in which the extensive report of the National Research Council about pesticides in the diets of infants and children plays a major role, is that children can be until 10 times more sensitive to the effects of pesticides than adults. The reason for this is often the greater vulnerability of organs that are still developing. Specific conclusions can only be made however per substance, on the basis of suitable data. Recent re-evaluations of (more extensive) toxicological data about pesticides in which these and other new insights have been taken into account resulted often in the establishment of a lower ADI.

In the risk evaluation both the susceptibility and the exposure to the pesticide residues are important aspects. In the USA the evaluation of possible other exposures to pesticides than via food is now mandatory, and the combined exposure to other residues also has to be considered. Children often will be the most exposed group, for various reasons. The methodology of this approach needs further elaboration, however. In Codex and also nationally methods have been introduced to estimate the exposure via food to pesticide residues, which incorporate using average regional, resp. national consumption data.

The consumption by children is for many foodstuffs 2-4 times higher than that by adults, expressed on a body weight basis. Some specific food commodities, such as milk, apples and bananas are to an even higher extent more consumed by children in relation to adults and form also a high proportion of the diet of children. Consumption figures of primary agricultural foodstuffs for various age groups have been calculated from the Dutch National Food Consumption Survey data, using the conversion model which was developed earlier by RIKILT-DLO. The results show that the consumption of most primary

products is highest for 1 year old children, when it is calculated on a body weight basis, and gradually decreases till the adult age.

The national theoretical maximum daily intake (NTMDI) was calculated for children of various age groups by using the international intake calculation model, for various pesticides. The results show that the ADI in the NTMDI-calculation was exceeded for most children in 3 out of the 4 cases, whereas for the average population only one exceeding was found. When it is assumed that the ADI for children has to be lowered by a factor 10, the NTMDI is exceeded to an appreciable extent for all pesticides that were examined. It has to be borne in mind however, that the NTMDI is only the first phase in the approach of the intake and as such is a gross overestimation of the real intake. There also is no firm scientific basis for lowering the ADI with a factor 10 as a general rule to take account of the possibly higher vulnerability of children. The 4 examined pesticides also mostly had fairly recently established ADIs and were known to be critical (except one) regarding their theoretical intake. More attention for the exposure of children to pesticide residues seems warranted, however.

The possibly greater susceptibility of children and their greater exposure to pesticide residues have until now probably received insufficient attention in the risk assessment and in the international and national policy regarding the registration of pesticides and the risk management of their residues. Though it does not seem likely that adverse effects have occurred in practice, because of the large safety factors, it is recommended that the various aspects of the possibly greater risk for children (both regarding chronic and acute exposure) are further investigated and that also the possibilities of improving the incorporation of these aspects in the risk management of pesticide residues are considered.

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SAMENVATTING

Er is een korte literatuurstudie gedaan naar de mogelijke effecten van residuen van bestrijdingsmiddelen op kinderen. De conclusie van de (voornamelijk Amerikaanse) literatuur, waarbij vooral het uitvoerige rapport van de National Resource Council over Pesticides in the diets of infants and children moet worden genoemd, is dat kinderen tot 10 maal gevoeliger kunnen zijn voor bestrijdingsmiddelen dan volwassenen. Reden hiervoor is veelal de grotere gevoeligheid van nog in ontwikkeling zijnde organen. Specifieke uitspraken hierover kunnen echter alleen worden gemaakt per stof, als voldoende gegevens ter beschikking staan. De indruk bestaat dat het verwerken van deze en andere recente inzichten in de toxicologische beoordeling van bestrijdingsmiddelen en het verkrijgen van meer complete dossiers vaak leidt tot de vaststelling van een lagere ADI.

Bij de beoordeling van het risico is naast de gevoeligheid voor een toxisch effect ook de mate van blootstelling van belang. In de VS is inmiddels ook het mede beoordelen van de effecten van blootstelling aan bestrijdingsmiddelen anders dan via de voeding verplicht, terwijl daarnaast rekening moet worden gehouden met de effecten van meervoudige blootstelling aan eveneens in de voeding aanwezige andere residuen en stoffen. Ook wat dat betreft kunnen kinderen om diverse redenen meer blootgesteld zijn dan volwassenen. De methodiek hiervoor is echter nog niet uitgewerkt. In de Codex en ook nationaal is de evaluatie in de praktijk beperkt tot de blootstelling via de voeding. Hiervoor zijn methoden uitgewerkt die uitgaan van de gemiddelde regionale of nationale consumptie.

De consumptie door kinderen is voor veel voedingsmiddelen een factor 2-4 hoger dan voor volwassenen, betrokken op het lichaamsgewicht. Enkele specifieke voedingsmiddelen, zoals melk, appels en bananen worden zelfs in nog sterkere mate meer gegeten door kinderen dan door volwassenen en hebben relatief een groot aandeel in het dieet van kinderen. Met behulp van gegevens uit de Nederlandse Voedselconsumptiepeiling en het door het RIKILT-DLO ontwikkelde conversiemodel is de inname van een aantal agrarische produkten berekend voor diverse leeftijdsklassen uit de bevolking. Hieruit blijkt dat de inname van de meeste primaire produkten, betrokken op het lichaamsgewicht, relatief het hoogst is voor de éénjarigen en geleidelijk afneemt bij het ouder worden.

De theoretische blootstelling van kinderen aan enkele bestrijdingsmiddelen is berekend met behulp van het hiervoor bestaande internationale inname-model, dat eerder door het RIKILT-DLO geschikt werd gemaakt voor het bepalen van de nationale theoretische maximale dagelijkse inname (NTMDI) van bestrijdingsmiddelen via de voeding. Uit de resultaten blijkt dat de ADI bij de NTMDI voor 3 van de 4 in beschouwing genomen stoffen voor kinderen meestal werd overschreden, terwijl dit voor de gemiddelde Nederlandse bevolking slechts éénmaal het geval was. Als wordt aangenomen dat de ADI

voor kinderen een factor 10 verlaagd zou moeten worden, is de theoretische overschrijding van de ADI in alle gevallen aanzienlijk. Hierbij dient overigens te worden aangetekend dat deze vorm van berekening slechts als een eerste, maximerende, benadering mag worden beschouwd en een ruime overschatting van de werkelijke inname met zich mee brengt. Verder was van de in beschouwing genomen stoffen bekend dat ze relatief kritisch zijn wat betreft residutoleranties en theoretische inname. De meeste stoffen hadden ook een recente ADI, zodat de noodzaak van verlaging van de ADI voor kinderen twijfelachtig is. Niettemin kan de conclusie worden getrokken dat meer aandacht voor de blootstelling van kinderen aan residuen van bestrijdingsmiddelen gewenst is.

De indruk bestaat dat de mogelijk grotere gevoeligheid en de relatief grotere blootstelling van kinderen tot nu toe onvoldoende in de risicobeoordeling en in het internationale en nationale beleid t.a.v. de toelating van bestrijdingsmiddelen en in het residubeleid zijn verwerkt. Hoewel het niet zeer waarschijnlijk lijkt dat er werkelijk schadelijke effecten hierdoor in de praktijk zijn opgetreden, vanwege de gebruikte grote veiligheidsfactoren, wordt aanbevolen om de diverse aspecten van het mogelijk grotere risico voor kinderen (zowel voor chronische als acute blootstelling) nader te onderzoeken en om na te gaan in hoeverre het mogelijk is in het residubeleid hiermee meer rekening te houden.

The report of the US National Research Council about pesticides in the diets of infants and children (1993) has led to a world-wide debate about the validity of the principles and practices used in the risk analysis of pesticide residues and to questions about the health protection in relation to the use of pesticides. It has led to regulatory changes and contributed to the establishment in the USA of the Food Quality Protection Act. In his introductory statement, president Clinton points to the fact that the existing regulatory system in the USA did not provide sufficient safeguards for the health of infants and children and was not adequate in maintaining a consistent standard for safety evaluation and for regularly reviewing older approved pesticides. It is therefore of utmost importance that this issue is also carefully considered in the Netherlands, that the scientific aspects are studied and presented in a transparent way, so that risk management options can be evaluated.

The main aspects of the debate concern the greater sensitivity of children to toxic substances and their greater exposure because of their higher food consumption in relation to their weight. Also specific dietary patterns of children may contribute to a higher exposure to food contaminants, whereas their non-food exposure can be higher too. Furthermore everybody is exposed to a cocktail of substances, some of them with the same mechanism of toxic activity. Again, children may be the first group to be at risk. It is questioned whether all these aspects are sufficiently taken into account in the present risk assessment and the risk management of pesticides.

This project is aimed at (shortly) describing the background and the arguments that are important in the risk analysis discussion and then focuses on calculating the exposure of children to pesticide residues according to an internationally accepted calculation model which is normally applied in the risk assessment of maximum levels for pesticide residues. The purpose of this calculation is not to obtain a realistic intake approximation, but to show the effect of applying consumption data for children and also of using a child-adjusted ADI, in relation to the results when average consumption data are used and the existing ADI.

This report consists of the following elements:

The present system of pesticide registration in the Netherlands and the underlying national and international risk assessment and risk management procedure are described in the Annex to this report, because a good knowledge of the principles used is necessary for understanding the discussion, whereas this information is familiar for those that are primarily involved with these matters. Chapter 2 gives an overview of the arguments used in the discussion about the risks of pesticide residues for children, based on the 1993 NRC-report, review articles and statements of government institutes and of various organisations on the World Wide Web.

In chapter 3 calculation results are shown in which the national theoretical maximum residue intake is estimated, using existing accepted methodology, for some selected pesticides, using maximum residue levels in food products according to the Dutch Pesticide Act and food intake information available from the recent Dutch National Food Consumption Survey (DNFCS). The effect of using these data is shown on the theoretical residue intake of children, compared to the calculated intake of the average population. Also, the effect of using a 10-fold lower (child-adjusted) ADI in the calculation is shown.

The results of the project are discussed in chapter 4.

Conclusions and recommendations are presented in chapter 5.

The project does not encompass calculations regarding age groups or other subgroups that were not covered by the DNFCS, implying that no calculations have been performed for children less than 1 year old. Also, no attempt has been made at this stage to perform more elaborate (and more realistic) intake estimations than the NTMDI.

The description of the argumentation, the discussion and the recommendations with a more general nature are for the responsibility of the first author.

2 OVERVIEW OF THE DISCUSSION ON PESTICIDE RESIDUES AND CHILDREN

2.1 Special characteristics and sensitivity of children to toxic substances

2.1.1 Differences between adults and children

The need for a special approach for evaluating the health risks from chemicals for children was already indicated by an expert group of the WHO (WHO, 1986). The NRC (1993) discusses the special characteristics of children and perinatal and pediatric toxicity in relation to pesticide residues in extenso. Other authors (Bearer, 1995, Goldman, 1995) have made useful overview articles on the subject. A short summary is given here.

Although this report is focused especially on children after they have been born, it will be clear that the health of children can already be influenced by the effects of chemicals on both parents, as far as the ovum and sperm are affected, and by effects of toxic substances on the pregnant woman. Many compounds readily cross the placenta, gain access to the fetal circulation and may cause toxic effects. Also substances in the amniotic fluid may be swallowed by the fetus or be absorbed via the skin, which lacks a protective layer of keratin until 3-5 days after birth.

Thus, a child at the start of its life, may already be carrying a body burden of chemicals and could be suffering their effects. After birth, chemicals get access to the body by absorption via the digestive tract, via the respiratory tract, or via the skin.

The absorption and metabolism of chemicals via the digestive tract of infants until several months old may be influenced by the low secretion of stomach acid; this is for example well documented for the risk of nitrate ingestion. Enhanced absorption through the intestine for children is known for calcium (needed for bone growth), but this also affects related metal ions like lead. In young children the intestinal flora can be different from that of adults, which can also be a reason for differences in metabolism and absorption.

The absorption through the respiratory tract is probably not essentially different between children and adults, but because of their greater activity and higher metabolic rate the oxygen consumption and in it's wake the uptake of airborne pollutants can be higher in relation to the body weight (about twice). Absorption through the skin is, after the first few days of the newborn, probably not essentially different from an adult, but again relatively it may be higher for a child because of the larger surface-to-weight ratio for a small body.

A major difference between children and adults is the relative immaturity of the biochemical and physiological functions of the body, especially for the fetus and to a lesser extent also for infants and young children, and the growth and development that is taking place. This can imply that detoxification

processes that normally play a role in the metabolism of an ingested toxic substance, are not yet functioning adequately, e.g. the development of conjugation enzyme activity. Another aspect is the growth of body organs, which can imply enhanced susceptibility to toxic effects. There are many critical stages of development of the body, during which the fetus or the child may be especially vulnerable to harmful substances. Toxic substances often have specific effects on functions or target organs of the body. Because of the growth and development process in which target organs or specific cells may be involved, the effects of that chemical on a child can be much more severe than on an adult and permanent damage could more easily be inflicted. Some organs continue to develop for several years after birth. Examples are the brain and the lungs, which are not complete until adolescence. In general the child's central nervous system (CNS) is vulnerable in its development for substances with an effect on the CNS, as many pesticides have. Obviously also the reproductive system develops further in a later life phase, so substances that mimic reproductive hormones can have a profound effect; chlorinated insecticides are an example of this mechanism. The endocrine system of children is considered more vulnerable to endocrine disruptors than that of the adult, and the same goes for substances with an effect on the immune system.

Other differences between children and adults are usually more a matter of differing size, composition and proportion of organs, body fluids and lipids and of the body in total, which can have an influence on the intake, absorption, distribution, metabolism, effect and excretion of the chemical.

A specific difference between adults and children is naturally also the larger life span that lies ahead of children. This can be significant for the apparition of toxic effects that require a long development, like tumors. EPA (1997c) has found from carcinogenicity studies that the incidence of tumors may increase and the latency period may be reduced when there was combined perinatal and adult exposure, compared to adult exposure only.

In general the susceptibility of children for toxic substances is thought by the NRC to amount up to a factor 10 higher than that of adults. This may be different however per substance or group of related substances, and more information is needed to gain a better insight in this matter. Specific judgment based on reliable data, per substance on a case by case basis, will be always needed for more firm statements.

2.1.2 Susceptibility of children to pesticide residues found in practice

The NRC mentions a number of examples that show that children may be more (in some cases: less) susceptible to the toxic effects of chemicals. Most examples concern medical drugs or contaminants, however. Specific data of this kind regarding pesticides are evidently scarce, and often are confined to non-food exposure or to food incidents, e.g. a case in Jamaica in 1976 where people were acutely

poisoned by eating parathion-contaminated flour. Case-fatality ratios were reported to be highest for young children (Diggory et al., 1977). Zahm and Devesa (1995) have reviewed specific case studies in which a link is made between pesticide exposure and cancers in children. Especially agricultural occupation of a parent, and parental use of pesticides in the home or the garden seems to be associated with cancers like leukemia, lymphoma and brain tumors. The reports suggest that children may be a particularly sensitive subgroup of the population with respect to possible carcinogenic effects of pesticides.

In a number of animal tests, higher susceptibility of young animals in relation to adults has been observed, e.g. in investigations on the LD₅₀. A greater sensitivity of young animals for organophosphates was demonstrated by e.g. Benke and Murphy (1975). In 1988 feminization of male fetuses was found for vinclozolin in rats, which eventually led to a lower ADI for this substance (Gray et al., 1994). Organochlorine pesticides like DDT have been associated with endocrine disruptive effects on wildlife, especially related to developmental toxicity. Although residues of organochlorine pesticides in human fat can be high and babies can receive high doses via mother's milk, no clear adverse effects have been found (these substances are in most countries already for many years forbidden for use, but due to their persistence in the environment some exposure remains).

2.2 Adequacy of present hazard assessment for children

2.2.1 Toxicity tests

Toxicity is tested by performing a number of trials in which the substance or preparation which is to be investigated is administered to laboratory strains of several species of animals. The NRC-report questions the adequacy of the tests as they are now required in the registration procedure of pesticides regarding their applicability for the health protection of children and recommends to develop toxicity testing procedures that more specifically assess the vulnerability of infants and children. Testing must be performed during the developmental period in appropriate animal models, and adverse effects that are encountered must be followed over a lifetime. Tests for neurotoxicity and for toxicity to the developing immune and reproductive systems are of particular importance. Taking proposed changes by the EPA into account, the NRC considers that current registration requirements do not (sufficiently) address the metabolism and the toxicity of pesticides in neonates and adolescent animals, and the exposure during early developmental stages (after the first trimester, through adolescence) and sequelae in later life. Some recommendations are made for general studies aimed at gaining more knowledge regarding vulnerabilities of young animals. Furthermore some specific recommendations are made for modifying present toxicity tests to improve the incorporation of the vulnerability aspects of young animals. This affects the chronic toxicity/carcinogenicity study, the

immunotoxicity test, the reproductive/developmental study. EPA proposals for the neurotoxicity testing are supported. A general guideline is mentioned to be needed for visual toxicity testing, that should be applied on a case by case basis. Also the Scientific Committee for Food of the EU (1997) considers that 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. We conclude that this matter needs further consideration by experts. The further development of various specific test guidelines is also on the agenda of the OECD test guideline programme.

2.2.2 Carcinogenicity

The issue of carcinogenicity deserves further specific review. The NRC devotes much attention to this matter, and provides indications that exposure early in life may be the largest risk factor for tumor development later in life. The risk estimation depends however on the cancerogenesis and tumor growth models that are used in the risk assessment. No clear proof seems to be available about actual carcinogenic effects of pesticides on humans and most experts conclude that there is no indication that pesticide residues in food contribute to cancer risk. The debate about the carcinogenic potential of pesticide residues is already for a long time a big issue in the USA. The EPA uses a mathematical low-dose risk-estimation procedure by which cancer risks are quantified by extrapolation in a linearized multistage model from cancer formation observed in test animals at higher dosage levels to low dose exposure situations. Although the EPA thinks this is a highly conservative approach, consumer groups claim it might still underestimate risks (Feldman, 1995). At the same time, in Europe most toxicologists are of the opinion that the cancer risks are overestimated in this way and that a difference should be made between primary cancer-inducing substances (genotoxic compounds) and tumor-promoters for which a threshold level can be found, below which there is no measurable cancerogenic activity. Because genotoxic substances are in Europe not allowed to be used as pesticides, and non-genotoxic tumor-growth promoters are only accepted for use when a safe threshold level could be found, as a result pesticides essentially pose no cancer risk. The differences in the approach are discussed by Renwick (1995), without drawing conclusions. The NRC mentions that the EPA estimates are believed by many to overestimate the cancer risk. On the other hand, the NRC thinks that the carcinogenicity studies as recommended by EPA may underestimate the risk from exposures incurred during infancy or childhood. Obviously further research and discussion is needed to resolve this matter.

2.2.3 Teratogenicity and developmental toxicity

Teratogenicity is a toxic effect that may occur in the early development phases of the child, before it is born. It has always been regarded as major health concern because it is an irreversible adverse effect

which can be induced by a single dose of a teratogen. For this reason usually an extra factor (mostly 10) is added to the normal uncertainty factors applied, when the toxicity data base shows indications of teratogenicity. Renwick (1995) mentions that the extra factor should be related to the NOAEL for the teratogenicity effect and not to a possibly lower other NOAEL (e.g. maternal toxicity), in order to apply such type of factors in a scientifically justified way.

Because a single dose can produce the adverse effect, the exposure assessment should be aimed at acute intake of residues.

Teratogenicity can be seen as a specific case of developmental toxicity and in general it seems appropriate that indications of developmental toxicity are regarded as major health concerns, which should be treated in a similar manner.

2.2.4 Susceptibility of children and ADI establishment

The ADI is a crucial element in the risk analysis, because it is the main criterion used to judge if pesticide applications can be allowed and if pesticide residues can be considered safe. The ADI in itself is not a quantitative risk estimation, but an exposure level which is considered safe during a lifetime. Most toxicologists are of the opinion that an ADI based on a currently accepted data base is valid for children, because reproduction and teratogenicity tests include exposure of the early development phases, and chronic toxicity studies at least include later developmental phases, while also the higher food intake per kg body weight is usually automatically incorporated in long-term studies in which young animals are tested (Lucas Luijckx et al., 1994). The WHO (1990) states that the entire age range of the population is normally covered by the ADI. The SCF of the EU (1997) is also of the opinion that the ADI should be valid for all sensitive segments of the population, irrespective of age. Still, the question whether an existing ADI can be applied to (all) children is open to discussion. Truhaut (1991), the "father of the ADI-concept", is of the opinion that the ADI-concept is not applicable *per se* to high-risk groups such as newborns and very young children. The NRC-report (1993) suggests that the risks for children have not sufficiently been taken into account in the risk assessment until now. This implies that improved toxicity tests could have an effect on the ADI that is established. The outcome of the results of toxicity tests that may be considered adequate for assessing the potential adverse effects on children on an ADI evaluation may vary, depending on the adequacy of the database that was the basis for the former ADI, and on the safety (uncertainty) factors that were used. It is therefore difficult to forecast whether and how existing ADIs for pesticides have to be changed, when comprehensive information on the toxic effects on young test animals would be available and would be used to establish ADIs that can be considered validated for children, according to recent views on this matter. Developmental toxicity is not always the crucial factor in the toxicity data base.

The present list of ADIs established by the JMPR is composed of evaluations performed during three decades and seems mostly to be fairly consistent according to the stated general principles and procedures of the JMPR; some inconsistencies however may exist (Lu, 1995). Based on some recent examples (FAO, 1996), it can be assumed that toxicological experts often tend to set a lower ADI when a pesticide is reevaluated. This need not be because of the risks for children per se, but mainly because a prudent approach is taken in setting the ADI. When additional risks have been shown to exist, when there was e.g. a critical NOAEL for reproductive performance, or when the data base is considered inadequate, a higher uncertainty factor was used for the establishment of the ADI. In other cases, more studies were available than for the evaluation of the previous ADI for the same compound, including studies with a lower NOAEL; because the same standard uncertainty factor was used in conjunction with a lower NOAEL, this also leads to a lower ADI.

2.2.5 Role of uncertainty factors in the establishment of the ADI

The uncertainty factors used in establishing the ADI as an extrapolation from the NO(A)EL play a major role in the outcome of the hazard characterization, because the factors are large and can vary, depending on the judgement of the expert group about the adequacy and consistency of the data base. Renwick (1991, 1993, 1995) has issued various publications in which the establishment of uncertainty factors is explained and in which proposals are made for a more standardized way of applying these factors. This can lead to higher uncertainty factors when the data base is considered incomplete, or in relation to the nature of the toxicity of the compound. Based on that line of thinking, it could also be envisaged that when more exhaustive tests would be available regarding the expected susceptibility of children, and would lead to a more firmly established NO(A)EL, a smaller uncertainty factor for the variation between humans could be used for the extrapolation of the ADI. After all, it is also common practice that when sufficient data on the toxicity of a substance on humans is available, this is used to drop the uncertainty factor of 10 for the extrapolation from animals to humans. This is a matter for future discussion, however.

In general it should be borne in mind that an ADI as such is not an absolute cut-off point between safe and unsafe exposure levels and therefore should not be seen as an indicator of the probable occurrence of adverse effects when it is exceeded. The ADI is simply a reference value that is considered to represent a safe level of intake at the time of the evaluation and on the basis of the available data. Because of this situation, especially "old" ADIs are liable to be changed (mostly: lowered) when they are reevaluated. Also, it can be concluded that the application of uncertainty factors is still in discussion among experts and risk managers should take note of these developments and partake in the discussion, because exceeding the ADI implies that risk management decisions have to be considered.

The NRC found that quantitative differences in toxicity between children and adults are usually less than a factor 10. This means that it may be expected that when the toxicity to children would not have been adequately assessed earlier, when an ADI for a pesticide was established, and when indeed developmental toxicity is shown, a new ADI taking account of this might be up to a factor 10 lower than the previous ADI. This principle has also been incorporated in new US legislation. For this reason the idea of using a 10-fold lower ADI as a possible "child-adjusted ADI" has been used by various authors (Schilter et al, 1996), and is also used in this study as a "worst case" example.

2.2.6 Implementation of recommendations regarding the susceptibility of children

The reactions on the recommendations of the NRC-report generally have been favourable. Progress is slow however in the implementation, especially outside the USA. In the USA, the new legal framework in the form of the Food Quality Protection Act, provides a good basis for demanding the necessary enhanced toxicological data base from pesticide manufacturers and for including the susceptibility of children in the evaluation. Further data about the application in practice have to be awaited however, before firm conclusions can be drawn.

The 1993 JMPR (FAO, 1993) concluded that toxicological information developed as a consequence of the NRC-recommendations would come available as data on individual pesticides submitted for consideration by future JMPRs.

2.3 Exposure assessment via food for children

2.3.1 Exposure assessment methods regarding residues in food and drinking water

There are severe methodological problems in adequately assessing the exposure of consumers to pesticide residues in food and water. The main reason for this is the complexity of consumption patterns on the one hand, and the complexity of residue patterns on the other. For the risk management of pesticides, predictive calculation methods are generally used. Methods available for assessing the residue intake in practice include total diet studies by analyzing duplicate portions of the diet as eaten or market basket studies, in which foods or food groups are analyzed after preparing them as they would have been in the average household and making composite samples in proportion to food consumption surveys. In the Netherlands this type of studies has been carried out by RIVM and TNO-Voeding, respectively. The results of these studies always were very reassuring, the exposure being in the range of a few percent of the ADI, usually even less. These studies have until now not been directed towards young children, however (de Vos et al, 1984; RIVM, 1987/1988),

or it is noticed that the exposure of children often exceeds that of adults, and it is recommended that future studies are concentrated on the younger age groups (Brussaard et al., 1996).

The residue intake can also be calculated, making use of available food consumption data and of residue data from registration dossiers (MRLs, STMRs, effects of processing), and/or using available monitoring and surveillance studies of pesticide residues in food products, mainly primary agricultural products as they are marketed. In this way, increasingly realistic calculations of residue intake can be performed in a tiered approach, described by WHO (1989) and Codex Alimentarius (1996). In the USA, this calculation approach is the main method. The application of this approach to calculate the intake of children is described by the NRC. In the Netherlands the methodology is ready in principle and there is both an extensive data base of monitoring studies and of consumption data. Actual intake calculations of pesticide residues have not yet been performed in full detail in this way, however. Further development of this methodology (especially regarding the necessary data on the effects of processing of primary agricultural commodities) and comparison of the results to those of total diet studies is desirable to develop this valuable instrument further.

2.3.2 Food and water consumption by children

The dietary consumption is usually the main route of exposure to pesticide residues and it is obvious that information about consumption patterns of children is necessary to assess the intake of residues by children.

There are various methods which can be used in the assessment of food consumption. In the Netherlands, recent results are available from the DNFCS, based on a household measure food record method in which the consumption of 2 consecutive days was recorded. This is not directed however to the diet of infants (children less than 1 year old). Data for this group are more scarce and less reliable. Further research is needed to establish suitable consumption data for children less than 1 year old, including individual variations, to be used in risk assessment.

The NRC uses the available data from US surveys and specific investigations (e.g. of infant nutrition surveys performed by industries supplying processed foods for infants and children); also in the USA specific information on the diet of infants and children is scarce. In order to be able to assess residue intake, the NRC converts the food intake expressed as processed or prepared products to primary agricultural products by means of the Dietary Residue Evaluation System (DRES), developed by EPA. This is necessary to be able to calculate the potential or actual intake, because MRLs and residue monitoring data are generally based on primary agricultural products. In the Netherlands, a comparable conversion methodology has been developed and is applied for residue intake calculations (van Dooren-Flipsen et al., 1995, 1996).

The available data show, as expected, that the food and water consumption of infants and children is much higher than that of adults, when it is calculated per kg body weight (bw). The overall intake of food per kg bw can be up 3-4 times higher than that of adults. Especially for infants and smaller children, the variety in the diet is less than that for adults, implying that the consumption of some specific food items is relatively high. Milk of course has a special position, but also other foods like apple (products), pears, orange juice, peaches, plums, grapes, bananas, carrots, oats, milled rice, soybean oil, coconut oil can be consumed in quantities that form a multiple (5-20 times) of the average consumption (expressed as percentage of the diet) (NRC). Peas, beans, broccoli, tomatoes, wheat, corn, sugar, eggs, beef, chicken, pork are also mentioned by the NRC as foods that can constitute a larger proportion in the diet of infants and children than in that of adults. Processed foods are predominant in the diets of younger age groups.

In a Dutch study (Löwik, 1996) the ratio of the mean consumption (expressed as g per day per kg body weight) of food groups was calculated for children (1-4 years) versus adults (aged 22-50 years). The ratio varied from about 1-10 for the different food groups and was 2-2.5 for vegetables, 4.4 for fruits, 2.4-4 for cereals and 7.4-10 for milk (products). This may be compared to the total energy intake, which is about 2.8 times higher for 1-4 year old children compared to the adult group. For older children the intake gradually approaches adult levels.

In this study, the total intake of specific primary agricultural products (including their occurrence in processed foods) could be calculated by means of the Dutch conversion model, using the same food consumption data base as used in the previously mentioned study. The results are mentioned in chapter 3.

The 1993 JMPR strongly recommended that governments address the need to have information about dietary patterns of population groups at risk, such as infants and children, by conducting appropriate dietary surveys.

The conclusion for the Netherlands is that food consumption surveys should pay specific attention to assessing the diets of infants and small children in a precise way and that residue intake estimations should take the intake data of infants and children into account.

2.3.3 Availability and use of food consumption data for exposure calculations

The Netherlands has with the DNFCs a good data base for assessing average daily intakes of the general population or of subgroups based on age, sex or social parameters. In this study mostly the average consumption by age groups is used in the calculations. The data on consumption are also suitable to assess short term intakes (portions or daily intake), but they are not suitable for assessing

other than average chronic consumption habits, because the variation within a dietary record data base of 2 days cannot be seen as representative of long term consumption patterns. For this reason a food frequency questionnaire will be added to the next consumption survey. When more extreme chronic consumption habits can be more reliably assessed in that way, the question remains how such type of information should be used in exposure assessment models. Obviously individual exposures can be calculated for situations in which the residue level is defined (e.g by using MRLs). Use of the outcome for risk management purposes may then require definition of a percentage of the population that might be allowed to surpass a given toxicological parameter (e.g. the ADI). The choice of the percentage should take account of the probably high degree of unreliability of the highest recorded consumption patterns.

A major problem regarding the use of extreme consumption patterns in risk assessment is that it is difficult to make general conclusions regarding diets that lead to high intakes of residues in food. Individual high consumption of one specific food will usually coincide with lower food consumption for other foods; adding all the high food consumption figures together will obviously result in a highly unrealistic model diet. It is therefore impossible to derive one single consumption pattern from the existing data base which is realistic as a chronic pattern and which at the same time can serve to calculate the highest possible exposures of individuals or subgroups. Also when more information comes available regarding more chronic consumption habits this will still be difficult to handle in relation to residue intake. Intake calculations with a data base containing this information might be possible as a national approach, but risk management decisions probably would need a method which can be used internationally and which can be visualised. Possibly more simplified high consumption models can be derived eventually, which could provide acceptable results in an international risk estimation model.

As a first phase, theoretical and more refined national exposure calculations for some substances, using the existing food consumption data base, will be useful to explore the results of taking other than average consumption patterns into account. Both chronic and acute intake evaluations should be performed, in order to assess the availability of the data and the applicability of the methods. Again, using the diet of children (as far as available) as a primary example, will be a logical choice.

2.3.4 Availability and use of residue data for exposure calculations

Data on residue levels always need careful interpretation because they are very dependent on the type of study to generate them, and also their validity can change quickly as use patterns of pesticides change. MRLs and STMRs are linked with residue analysis results of field trials in relation to pesticide

use. Apart from the MRLs that are made public because they are incorporated in the legal framework, this type of residue data is only available in dossiers in relation to pesticide registration.

Data on pesticide levels in foods in commerce in the Netherlands are mostly produced by the State Inspectorate for Health Protection and some other institutions, as a result of monitoring and control activities. Care in the interpretation of this type of data is necessary, because the sampling may not have been representative, in relation to control and enforcement priorities. Dutch residue data that may be considered to represent unbiased monitoring are assembled in the KAP databank and are readily available (KAP, 1997). This type of data is mostly directed to primary agricultural products as they are defined legally (because they are meant to be compared to the MRL for that product). This may imply that the levels in the food as eaten can be quite different (usually much lower, as a result of e.g. peeling and processing). The latter type of data is again more difficultly available (either lacking or in registration dossiers).

For infants, information on residues in infant formulas and infant foods is desirable. This type of information is only scarcely available in the Netherlands. Information from the USA is provided by Yess et al (1993). Gelardi et al (1993) explain reasons for the usual absence of pesticide residues in infant formulas.

For acute effects, information on possible unit-to-unit variation is relevant (normal residue data being based on composite samples that are blended to be representative for a lot); this type of information is only very seldom available, because the need to generate this type of data was only realised recently and special investigations have to be performed to collect the data.

Calculating exposure with MRLs is in itself an easy approach, which evidently leads to extreme overestimation of the (chronic) exposure in the form of a TMDI. The next step, involving the use of STMRs, and reduction factors based on the residues in the edible portions and the effect of processing, will necessitate reviewing existing data bases or further research because now often not sufficient data are available. This calculation can be done at the international level (IEDI) and will probably also have to be performed nationally (NEDI). Further theoretical reductions based on information from use patterns in practice, portion of foods that is imported etc. are possible, but will be more difficult to assess and will always be rather variable.

A specific problem in calculating the chronic intake is the way of dealing realistically with MRLs established on the LOD (LOQ). This has become more difficult since Dutch and EU regulatory practices do not (any more) make a difference between MRLs at the LOD based on registered use of the pesticide (without causing residues above the LOD), and MRLs at the LOD based on zero tolerance principles.

When still more realistic exposure calculations are desired, a link has to be made with the data which is available from the monitoring results of pesticide residues. The use of this type of information in assessing calculated intakes of pesticide residues will lead to further insight in the actual exposure pattern and therefore in the actual risks involved. Further decisions are necessary however on the methodology to be used.

One of the problems in the exposure assessment is of course that when the step is made from using a simple figure like the MRL, the STMR or the reduced STMR (after application of reduction factors), to using actual residue patterns, the calculations about exposure can become very complex. Two statistical distributions (consumption data and residue data) then have to be combined (convoluted). Results can be simplified by using average monitoring results; this was the EPA-approach until now. That approach was criticized by the NRC for not giving an adequate assessment of real intake. Performing the calculation in full detail will result in statistical probability distributions of residue intake quantities. The necessary amount of computing is then very large; a more simplified approach yielding a comparable result is possible (Monte Carlo approach). This method was applied by the NRC. A somewhat modified approach (Joint Distributional Analysis) is described by Petersen et al (1994).

A specific case is the calculation of short term (acute) exposure. The food consumption data used for this purpose has to take account of possible high individual consumption within a short time (CAC, 1996). On the residue side, information on MRLs alone, or on monitoring results, may not be enough, because individual portions of a food might contain higher residues than the MRL or than monitoring results (which both are based on composite samples). This unit-to-unit variation deserves further study in order to gain better insight in the situations where this might be applicable. National short-term intake patterns can be extracted from the DNFCs. Calculation of acute exposures is until now only meaningful for the small group of substances for which an ARfD has been estimated.

2.3.5 Results of exposure assessment and use of calculations in risk management

As mentioned in chapter 2.3.1, national total diet studies are until now not directed towards children or are only very limited in scope regarding pesticide residues. The relevance of these studies for possible problems regarding the exposure of children is therefore limited. It is recommended to pay more attention to children's diets in future total diet studies.

In the USA, the available monitoring results of pesticide residues in foods eaten by infants and children was described by Yess et al. (1993). These data are used for assessing the intake of (a.o.) children; the conclusion is that the average intake was in most cases less than 1 % of the ADI for all age groups.

Results of the FDA total diet study (Gunderson, 1995) show that the intake of pesticide residues by 2 year old children is usually 2-4 times higher than that for adults (calculated on body weight basis). The intake of children between 6 and 11 months of age is mostly less than for the 2 year olds; in some cases however the infants had the highest intake. All analyzed results (covering 120 analytes) were well below the ADI. The NRC calculated the intake of benomyl for children, utilising various residue data sets. In all calculations, the exposure was found to be well below the RfD (ADI) for benomyl. The calculated acute intake of aldicarb is mentioned in more detail in chapter 2.3.6.; it was found that the US-RfD could be exceeded.

The main advantage of exposure assessment calculations in which MRLs or monitoring results are used is that they can more easily include worst case situations and therefore give a better view of the maximum risks involved. They also can be used as a risk management tool, because the effects of management decisions can be calculated. In order to use this tool adequately, insight is necessary in the possibilities and the problems of this methodology. Extreme consumption patterns, which may lead to the highest calculated exposures, are probably rather unreliable. It may therefore be necessary to define a statistic parameter for the percentage of the population or for the food intake which will be included in the calculations leading to a decision scheme in the risk management of pesticide residues. Before such a decision is taken, the degree of realism of the calculation models has to be assessed. For this reason, detailed calculations will have to be made at least for some cases which can be used as an example. It will be worthwhile to strive for some parallel exposure assessments by applying different assessment methods to the same residue. Comparison with results obtained by duplicate diet studies and market basket studies will be useful for analyzing the methodological problems for increasingly realistic exposure prediction models. Especially the effects of processing on the residue content, from primary product to the prepared product as eaten, will have to be taken into account to arrive at realistic exposure levels. Because the information on processing effects for specific residues is often rather limited or even absent, this may form an obstacle for a realistic calculated intake estimation.

Because of the described complexities, a fully detailed type of calculation approach will probably have to be confined to some examples in which the link between the various methods to assess exposure is studied. For routine risk management purposes, a calculation model which assesses the maximum realistic dietary exposure in connection to proposed MRLs will probably be suitable (and necessary, for health protection reasons), while the other type of exposure assessments (duplicate diet and market basket studies) may still be useful in showing that the actual exposure is much less than the models used in the risk analysis, so that further safety factors are present.

2.3.6 Examples of practical problems related to pesticide residues and children

Aldicarb residues in watermelons and cucumbers (caused by illegal use) are known to have produced illness in North America in 1985, but there is no data about the effects on children. Calculations showed that children could be at risk also from residues derived from approved uses on bananas and potatoes, because of their higher exposure on body weight basis (EPA, 1988; Goldman et al., 1990). Aldicarb is a systemic pesticide for which in individual products sometimes up to 10 times higher residues are found than the MRL; for this reason especially children could consume quantities that might cause an effect and e.g. use on bananas and potatoes has been withdrawn therefore. The NRC (1993) presents a case study of the calculated acute dietary exposure to aldicarb for children, based on residues found in single commodity surveys in bananas and potatoes. The results indicate that the 95th percentile of children between 1 and 2 years was still below the 1992 EPA-RfD of 1 µg/kg but higher than the earlier EPA-RfD of 0.2 µg/kg. The WHO-ADI and ARfD for aldicarb are both at 3 µg/kg. It is apparent from the figures that exceeding the RfD and also the ARfD occasionally is possible; exposures reaching toxic levels will be a very rare event, but the fact that they cannot be ruled out remains a heavy burden for risk managers and explains the discontinuation of these previously approved uses.

Daminozide (brand name Alar) was used on apples as a crop ripening regulator and came in discussion in the USA because of supposed carcinogenicity in 1989. It developed into a major food scare, in which especially the risks for children were a strong argument. The sale of apples suffered losses of hundreds of millions of dollars and the use of Alar on apples was withdrawn late 1989 in the USA and later in the rest of the world. The toxicological discussion about the real risks never ended in a consensus, however; although Codex MRLs for daminozide in apples have been withdrawn because there is no longer registered use, the 1991 JMPR confirmed the ADI established in 1989.

2.4 Other types of exposure, especially related to children

Some specific aspects of the situation and the behaviour of infants and small children may lead to higher exposures to pesticides (other than via food), than is to be expected for adults (Bearer, 1995). For example, they often are placed and/or crawl around on the floor, on a carpet, on the soil or on grass. When pesticides were applied there in the past, these children would be exposed more than an adult would be. The breathing zone of a young child is much lower to the ground than that of an adult, and the child may be therefore more exposed to dust and breathable particulates in general. Pesticides that become airborne often assemble on small particulate matter and concentrations in dust can be quite high. Young children tend to eat and chew all kinds of articles (including soil) and also their hand-to-mouth behaviour may lead to enhanced exposure. Contact with pet animals that carry

flea collars or have been treated otherwise with ectoparasitocides are another source. Contact with treated plants and fields is another possibility which for active children is more likely than for adults. Reports from specific cases are not readily available from the literature, however. Bradman et al (1997) report high concentrations of a number of pesticides in house dust from rural children's home environments and calculate exposures which in one case exceeds the ARfD.

The 1995 JMPR considered the possible processes of risk assessment to be used for exposures of consumers other than dietary exposure. Many problems were seen, such as:

- integration of multiple routes of exposure
- "seasonal" occupational exposure
- route-to route extrapolation of results of toxicological studies

The Meeting decided to contribute to the process of assessing risks from different sources by tabulating the relevant data for each pesticide in a format designed to draw attention to the crucial toxicological results relevant to human exposure.

The new Food Quality Protection Act of the USA requires aggregate exposure assessment, meaning that pesticide exposure from all sources should be combined in the evaluation. Because the methodology to perform those assessments is not yet fully developed, an interim approach will be used in which chronic, acute, short-term, and intermediate-term exposure will be assessed by combining dietary, drinking-water, and residential (indoor and outdoor) exposures into an aggregated exposure. Occupational exposure will not be used for the purpose of tolerance-setting. When insufficient data is available, default assumptions will be used (EPA, 1997).

The question whether these other types of exposure should somehow be incorporated in risk evaluations is not only a scientific issue, but also a matter of risk management. In general, it will be necessary to pay more attention to the specific risks involved with the exposure of children via other ways than food. When there are convincing arguments that specific situations pose an unacceptable risk, appropriate national or local risk management measures to remove this risk will be necessary. When the situation is not so menacing, a difference can be made between quantifiable risks and other cases. Where it seems unlikely that a reasonable average intake can be attributed to this type of exposure, it is probably the best to rely on the existing uncertainty factors for the general safeguard regarding this issue, whilst in cases where there is evidence of a quantifiable other exposure risk, an appropriate portion of the ADI and/or ARfD could be set aside for this reason (as has been done for residues in drinking water). Further (literature) research is necessary to gain more insight in this matter and to identify possible cases where action might be appropriate.

2.5 Multiple exposure to substances

Risk analysis of pesticides is presently always carried out on a case by case basis, because information about the toxicology of a chemical is usually confined to tests on the effects of that chemical alone. Only when there are common residues, the MRL must take account of residues coming from more than one source and risk analysis must cope with the problem of a combined set of MRLs originating from several substances. In practice, consumers are exposed to multiple residues in their diet. Even within one commodity, more residues can be present, because many pesticides may have been registered for use to protect the plant from various diseases and pests. In principle, multiple residues may be expected to have an additive influence on each others' effect, when their mode of action is related. Synergistic, but also antagonistic activity is also possible, however. The knowledge about the effect in practice is very limited at present, and deserves further study. Ito et al. (1995) found that 20 pesticides ingested in combination, all at the level of the ADI, did not have an effect on rat liver carcinogenesis, suggesting that the ADI-concept provides sufficient safety. Potentiation by unrelated chemicals has been shown for a combination of permethrin and DEET (an insect repellent) (Jensen, 1996). The resulting neurotoxicity was markedly greater than that resulting from treatment with any individual compound.

A number of pesticides are very related in their toxic effects, notably the organophosphates that inhibit cholinesterase. The NRC (1993) discussed the topic and estimated the combined intake of residues of 5 organophosphorus pesticides, using regular monitoring data on their presence in foods. The different residues were combined by adding them after correcting the concentrations to a common standard by applying a Toxicity Equivalence Factor based on comparison of NOEL or LOEL levels. In that calculation 1.3 %, resp. 4.1 % (when fruit juices are included) of the estimated person-day exposures of 2 years old children were calculated to be above the ADI (RfD). The development of further refined and validated risk analysis methods for combined exposure to pesticide residues is recommended by the NRC.

It is acknowledged that the issue of dealing with multiple exposure to residues is not confined to children. The fact that children are probably the most exposed and the most vulnerable group makes clear however that the risks involved with multiple exposure and the risk management policy towards this problem is likely to affect children the most and therefore inevitably becomes part of the discussion about the risks of pesticide residues for children.

The 1981 JMPR mentions the fact that in principle all compounds present in food can interact, so the possibilities are unlimited and the JMPR sees no reason why the interactions of pesticide residues (which occur at very low levels) should be of particular concern. Very few data on these interactions are available, and the data obtained from acute potentiation studies are thought to be of little value in

assessing ADIs for man. The 1996 JMPR concludes that the outcome of possible interactions (which can vary between enhanced, mitigated or additive toxicity) cannot be predicted reliably. The safety factors that are used for establishing ADIs should provide a sufficient margin of safety to account for potential synergism.

EPA is required by the new Food Quality Protection Act to perform combined risk assessments for chemicals that produce adverse effects by a common mechanism of toxicity, relying on available data for decision making. Procedures for this evaluation, which will be extremely complex are being developed and will, besides the structure activity relationships (SAR) and toxicity test results, also involve the evaluation of expected concurrent exposures. The evaluation of the effects of complex exposure patterns to toxic chemicals will lead to cumulative risk assessment (EPA, 1997b).

In the Netherlands, the issue of multiple exposure was evaluated by the Health Council/Gezondheidsraad in 1985, in their report about principles for the establishment of health standards. It was concluded that safety factors have to cover also the risk of multiple exposures and possibilities of interaction.

2.6 Implementation of procedures for improved risk assessment and risk management for pesticide residues regarding children

In principle a consistent procedure has to be followed in which risk management decisions are taken based on adequate risk assessment and sufficient health protection standards, taking the risks for children into account. These elements generally are incorporated in the laws governing pesticide registration and in legal provisions regarding pesticide residues, although the risks for children usually are not specifically addressed. In practice, decisions to apply the legislation are never easy. Existing situations can be fairly complex and great economic interests may be at stake, while on the other hand public perception of risks can have a great influence on decision making.

In the USA, public pressure to reform the pesticide policy in order to take the risks for children into account has led to activity of the EPA to incorporate the recommendations of the NRC into their risk assessment and risk management system (Fenner-Crisp, 1995) and to new legislation. In his introduction of the new Food Quality Protection act, the President commented (1996) specifically on the vulnerability of children and on the high protection standard that is aimed for. Major issues in the Food Quality Protection Act include the introduction of single, health-based standards for all pesticide residues in all types of food, resolution of the "Delaney Paradox", special provisions for infants and children, development of a screening program for endocrine disruptors, consideration of pesticide benefits, consideration of other factors for setting tolerances, consumer "right to know" provisions, re-

evaluation of existing tolerances, consideration of international standards for pesticide residues, national uniformity of tolerances and residue monitoring provisions and penalties for violations of tolerances. The FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act) also received amendments aiming at improving the periodic review of all pesticide registrations, expediting review of safer substances and improvements for a number of specific problems. The implementation of the various provisions that require further development of information and of procedures is explained by EPA (1996). The legislation provides the basis for applying an extra safety factor (10, or less when the evidence shows no specific vulnerability of children) to ensure that there is reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue.

The new US legislation has been criticized as bringing not only improvements regarding safeguarding the health of children, but also introducing aspects that can work in the opposite direction (EWG, 1996a).

In any case, the new US legislation will be both a useful example for the possibilities to implement more specifically the risks for children in the risk assessment and management of pesticides, and will also be an incentive to take appropriate action in other countries.

A specific approach regarding risk management related to pesticide residues and children is to define specific low residue tolerances for foods destined for children. This type of legislation exists in Germany and is in discussion within the EU. The Scientific Committee for Food has recently (1997) expressed its opinion that a level of 0.01 mg/kg in manufactured infant formulae and ready-to-eat weaning foods gives sufficient safety for pesticides with an ADI higher than 0.0005 mg/kg bw. This issue is shortly also discussed in paragraph 4.1.

3 CALCULATION OF THE THEORETICAL INTAKE OF PESTICIDE RESIDUES BY CHILDREN

3.1 Material and methods

Databases of the Dutch National Food Consumption Survey (DNFCS, 1992) and MRLs as contained in the Dutch Residue Regulation have been used in conjunction with the Conversion Model for Primary Agricultural Products in estimating the National Theoretical Maximum Daily Intake (NTMDI) of the residues of some selected pesticides for several age groups of children, in comparison to adults and the average population.

3.1.1 Dutch national food consumption surveys

The food consumption data used in this study come from the Dutch National Food Consumption Survey (DNFCS). These large-scale surveys were carried out in 1987/88 (DNFCS-87/88) and repeated in 1992 (DNFCS-92). Respondents in these surveys came from a representative sample of households with the main housekeeper younger than 75. A total of 5,898 people (2,475 households), aged 1-85 years, participated in the DNFCS-87/88. The second DNFCS-92 comprised 6,218 people (2,203 households), aged 1-92 years. Information on food consumption was obtained using a 2-day dietary record. The DNFCS was distributed equally over the 7 days of the week, and over a whole year, holiday periods excluded. For each individual age, sex, body weight and a series of other characteristics are recorded. The methods and procedures used in dietary data collection are described in detail elsewhere [Hulshof et al., 1991; Anonymous, 1994]. Briefly, in each household, the subject principally responsible for domestic affairs (the housekeeper) was the most important informant. The housekeeper carefully recorded in the household dairy all food supplied to the members of the household. The food consumption data were coded with the Dutch NEVO-code [Foundation NEVO Dutch Nutrient Databank].

For this study the consumption data of the DNFCS-1992 are used.

3.1.2 Conversion model Primary Agricultural Products

In the Netherlands, the government and agribusiness intensively monitor (raw) agricultural products for residues and contaminants. The (inter)national legislation sets standards for primary agricultural products. On the other hand in food consumption research, consumable products are registered. In 1994 the State Institute for Quality Control of Agricultural Products (RIKILT-DLO) developed a conversion model to unequivocally couple primary agricultural products and consumable foodstuffs [Dooren-Flipsen et al., 1996]. With this model it is possible to translate DNFCS-data (with data on consumption of foods as consumed) into data on consumption of raw agricultural products, so that the

basis for consumption matches that for residues. Furthermore this model offers the possibility to derive consumption figures for individual components of primary agricultural products such as milk fat, egg fat. Food consumption data of the DNFCs-92 were transformed into consumption data of (fat components of) primary agricultural products. For the construction of this raw agricultural commodity consumption database, containing consumption figures of 6,218 individuals, the Conversion model Primary Agricultural Products was used.

3.1.3 Dietary intake calculations

In the present study the national theoretical maximum dietary exposure (NTMDI) to residues of 4 different pesticides is assessed using combinations of the mentioned information sources (paragraph 3.1.1, 3.1.2 and 3.1.3).

For each individual (n=6,218) in the food consumption survey the daily intake was calculated by multiplying the amount of consumed product with the MRL of that product, and adding up the calculated residue intake of the different products consumed. MRLs at the LOD were not involved in the calculation. The individual intake of the residue, based on the 2 days dietary survey was calculated and expressed as intake per day ($\mu\text{g}/\text{day}$). For calculating the intake per kg body weight per day ($\mu\text{g}/\text{kg bw}/\text{day}$) the individual (self-mentioned) body weight of the person was used.

Calculations were carried out for age-sex groups in conformity with the classification of the Dutch Recommended Dietary Allowances [Netherlands Food and Nutrition Council 1992]. Further calculations for the total group of men and women and for the subgroups per year of the 1-10 year olds were performed. Descriptive statistics for the various populations were calculated.

Further the contribution of products and product groups to the total average daily intake from food was calculated. For this the total intake of all products of one category of food from all subjects is calculated and expressed as a percentage of total intake of all products by all subjects.

The criteria for choosing the pesticides were various. It was thought useful to include at least a few pesticides of which the theoretical maximum intake was expected to be critical. Another criterion was that various classes of pesticides and various MRL-patterns should be represented, to investigate the effect of these variations on the outcome of the calculations. The chosen pesticides were aldicarb, iprodion, carbaryl and fenvalerate. Aldicarb has relatively high MRLs for potatoes and bananas and is in discussion for acute toxicity aspects. Iprodion has high MRLs for a range of fruits and vegetables; its ADI was recently lowered (1995). Carbaryl also saw its ADI recently lowered (1996), and might be expected to exceed the ADI excessively in a TMDI-calculation because of many high MRLs (including in chicken meat and eggs). Fenvalerate on the other hand is a reasonably unchallenged compound (TMDI lower than the ADI), with real-level MRLs for milk and meats. The MRLs that were used in the calculations are the Dutch national MRLs (as contained in the Regeling Residuen van

Bestrijdingsmiddelen, as lastly changed 12 may 1997). The ADIs are those as lastly established by the JMPR and are mentioned in the text.

3.2 Results

3.2.1 Consumption of primary agricultural products by children in relation to the average population

The results of the calculation of the top 20 of the primary agricultural products that are included in the diet of various age groups of young children (either as the product as such, or in processed form) are given in Table 1. The results are expressed as consumption per kg body weight (not as individual intakes, but related to the average body weight of the age group). Also the ratio of the food product consumption of that age group versus the consumption of the average DNFCs-population is given. The figures were not corrected for wastage and have to be interpreted with caution. Water is in two items part of the top 20, but was left out in Table 1 (both as tap water and as added water contained in beverages). Items that were not always represented in the top 20 are mentioned as .. when no figure was calculated.

Table 1 Most consumed primary food commodities, in g/kg bw/day

Product	Age group (in years)					(all) DNFCS	Highest ratio to DNFCS
	1	2	3	4	5		
(cow's) milk	40.8	34.3	28.4	26.1	25.7	6.5	6.3
apple	7.2	7.0	7.0	6.7	4.6	1.3	5.5
potato	7.1	6.3	6.9	5.4	5.9	2.8	2.5
wheat	5.1	4.7	4.5	4.4	4.3	1.9	2.7
sugar	4.5	4.6	4.2	4.0	3.8	1.0	4.6
banana	3.4	2.3	1.7	2.2	1.3	0.3	11
orange	2.8	2.8	2.6	2.0	2.3	1.2	2.3
meat of pig	1.7	1.6	1.9	1.6	1.4	0.9	2.1
meat of cattle	1.4	1.1	1.1	1.0	1.1	0.7	2.0
mandarin etc.	1.1	0.8	0.7	..	0.7	0.2	5.5
milk fat	1.0	0.8	0.7	0.6	0.6	0.3	3.3
grapes (table)	1.0	1.2	0.8	0.5	0.7	0.2	6.0
grapes (wine)	-	-	-	-	-	0.5	1.7*

pea (fresh)	0.9	..	0.7	0.5	..	0.2	4.5
tomato	0.8	0.7	..	0.5	..	0.2	4.5
carrot	0.8	0.2	4.0
egg	0.7	0.9	1.0	0.8	0.8	0.3	3.3
veg.oils & fats	0.7	0.8	0.9	0.8	0.7	0.3	3.0
cauliflower	0.7	0.6	0.6	..	0.6	0.2	3.5
pear	..	0.6	..	0.7	..	0.2	3.5
veg. & anim.oils	0.8	0.6	0.6	0.3	2.3
spinach	0.6	0.2	3.0
meat of chicken	0.5	0.5	0.3	1.7

* Ratio calculated on total grapes consumption

The results show that the highest ratios are in most cases found in the 1-year olds. Only for some products the maximum consumption per kg body weight comes somewhat later in age (meat, eggs, fish). The largest relative difference in consumption between children and adults is found for bananas (ratio 11); other substantial differences occur for milk (6.3), apples (5.5), peas (4.5), carrots (4), cauliflower (3.5) and spinach (3). Other differences are more in line with the general difference due to the higher energy consumption of children, which is ca 2.8 times higher than that of adults. Products like meat, eggs and tomatoes are consumed less than this energy ratio. This reflects the differences in the diet of children from that of adults. For grapes, the higher consumption of table grapes by children is compensated by the intake of wine by adults, so that the total grape intake of children is not much higher than that of an adult.

In absolute figures, the main primary food commodities of Dutch children are milk, apples, potatoes, wheat, bananas, oranges and the various meats (mainly pig, beef, chicken). The intake of these main food commodities for children aged 1-5 years is also given in figure 1.

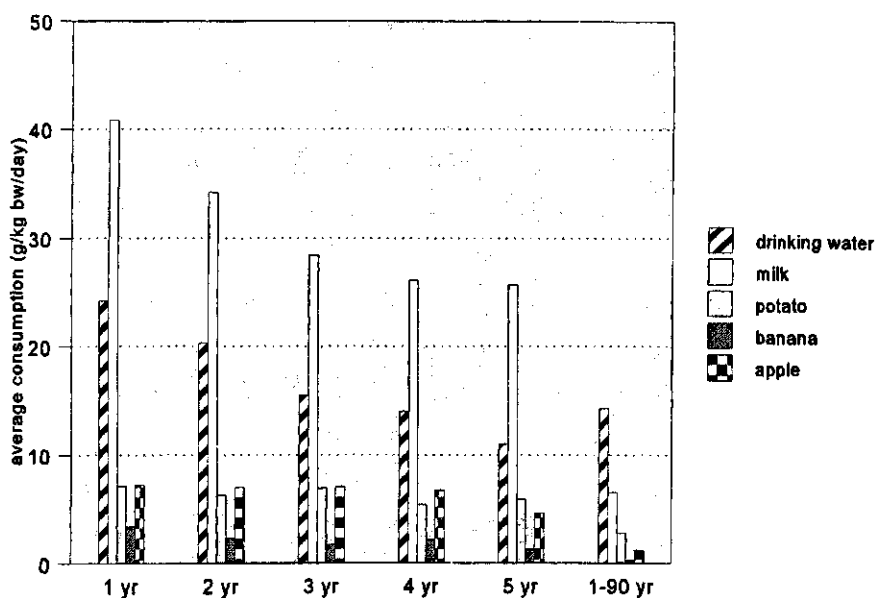


Figure 1. Consumption of primary agricultural products (g/kg bw/day).

3.2.2 NTMDI-calculations

Aldicarb

Figure 2 shows the results of the NTMDI-calculation expressed as percentage of calculated ADI-exceedings, both for the normal ADI ($3 \mu\text{g/kg bw/d}$) and for the 10-fold lower child-adjusted ADI, for the age groups 1-10 years and for adults. Figure 3 shows the same results as absolute figures. The continuous decline from the highest exposure on a body weight basis for 1 year olds to adults is clearly visible. The highest average aldicarb intake is found in the group 1-4 year old girls, with $5.7 \mu\text{g/kg bw/d}$. Compared with the calculated average intake of the DNFCs-population of $2.3 \mu\text{g/kg bw/d}$, that is a factor 2.5 higher, somewhat less than the difference in energy intake. The highest contribution for adults comes from potatoes, followed by citrus fruits and bananas. For young children, the contribution from potatoes and bananas is dominant. Compared to the ADI of $3 \mu\text{g/kg bw/d}$ the average TMDI of the 1-4 year old girls is 2 times higher. When the ADI would be lowered by a factor 10, this figure becomes 19.

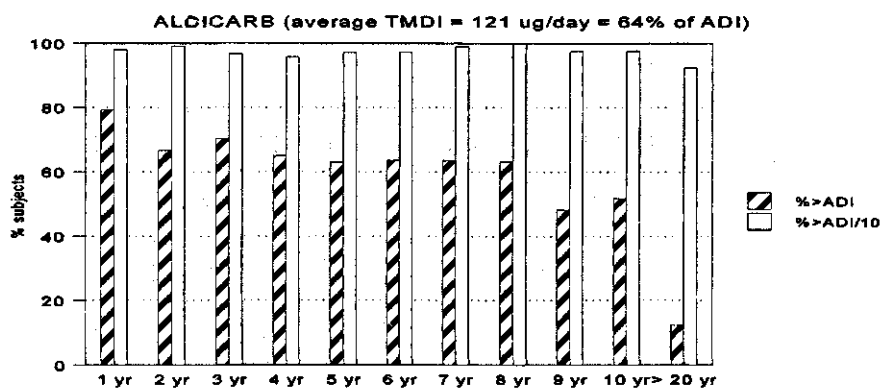


Figure 2. Percentage of subjects with a TMDI exceeding the ADI or lowered ADI, for different age-groups.

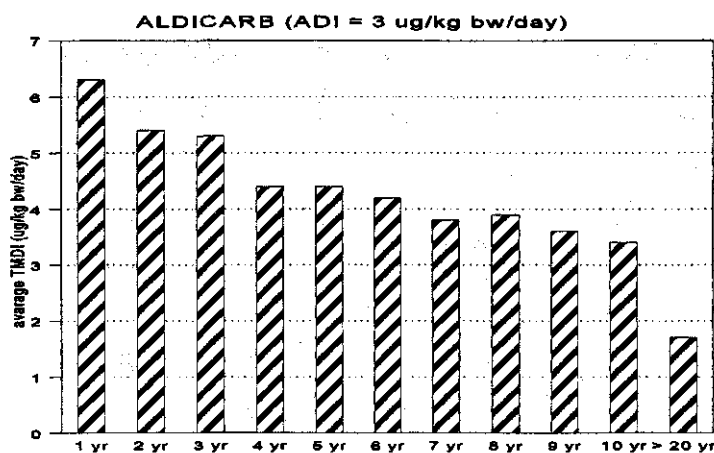


Figure 3. Average TMDI ($\mu\text{g/kg bw/day}$) for different age-groups

Iprodion

Figure 4 shows the results of the NTMDI-calculation expressed as percentage of calculated ADI-exceedings. Figure 5 shows the same results, as absolute figures. The frequency distribution of the intake for the whole DNFCS-population is shown in figure 6 and for 1-5 year old children in figure 7. It should be borne in mind that the frequencies recorded in the DNFCS represent the distribution of the average of 2 days of individual intakes, not of the chronic intake pattern. The highest average iprodion intake is found in the group 1-4 year old boys, with $128.5 \mu\text{g/kg bw/d}$. Compared with the calculated average intake of the DNFCS-population of $48.9 \mu\text{g/kg bw/d}$, that is a factor 2.6 higher, somewhat less

than the difference in energy intake. The highest contribution for adults comes from apples, followed by grapes. For young children, the contribution of apples is highly dominant, followed at a distance by grapes and carrots. Compared to the ADI of 60 $\mu\text{g/kg bw/d}$ the average TMDI of the 1-4 year olds is a factor 2.1 higher than the ADI. When the ADI would be lowered by a factor 10, this figure becomes 21.

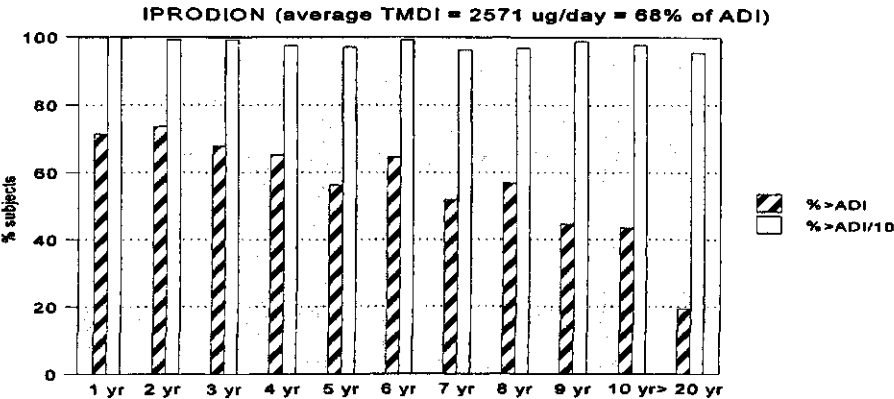


Figure 4. Percentage of subjects with a TMDI exceeding the ADI or lowered ADI, for different age-groups.

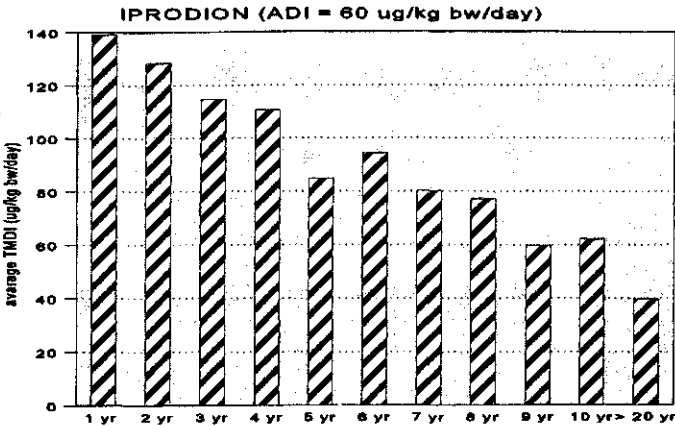


Figure 5. Average TMDI ($\mu\text{g/kg bw/day}$) for different age-groups.

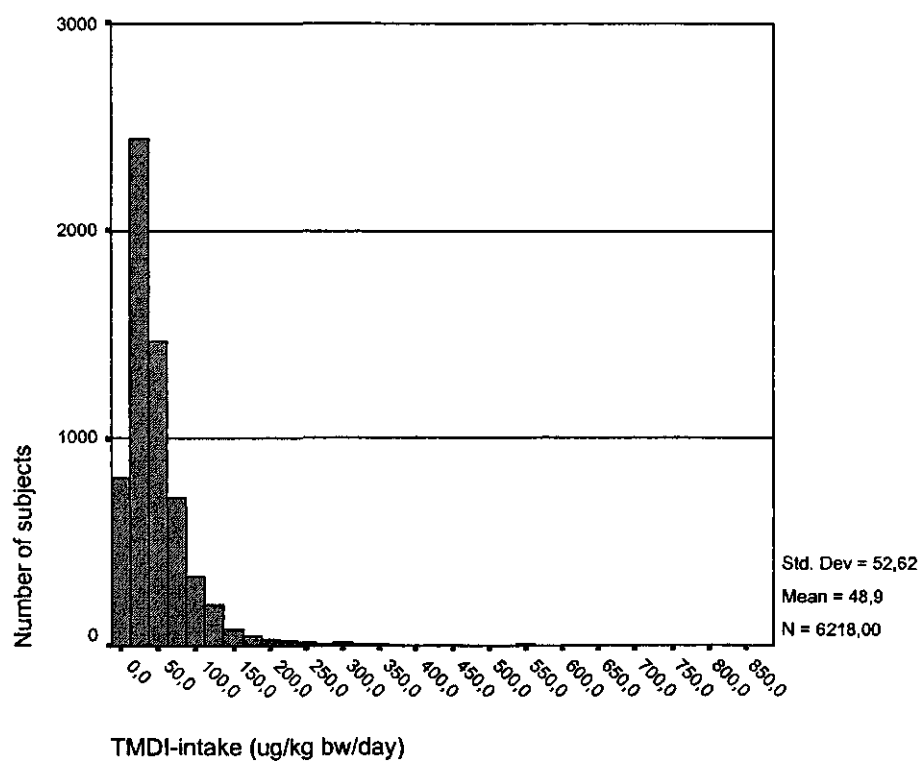


Figure 6. Frequency of TMDI iprodion total DNFCS-population (n=6218).

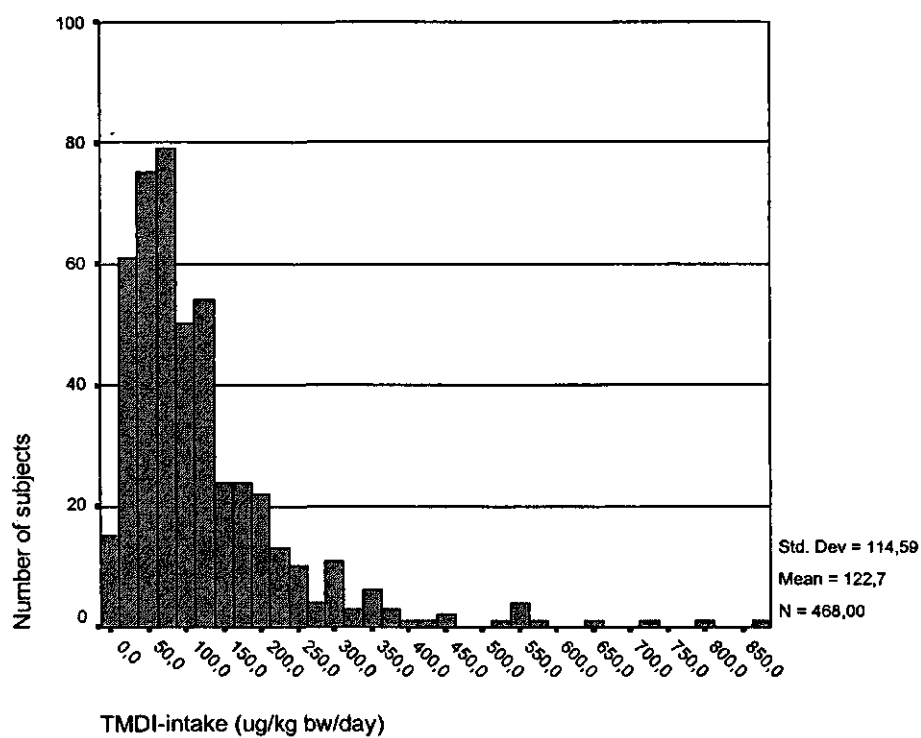


Figure 7. Frequency of TMDI iprodion population 1-5 years (n=468).

Carbaryl

Figure 8 shows the results of the NTMDI-calculation expressed as percentage of calculated ADI-exceedings. The highest average carbaryl intake is found in the group 1-4 year old boys, with 53.5 µg/kg bw/d. Compared with the calculated average intake of the DNFCs-population of 21.8 µg/kg bw/d, that is a factor 2.5 higher, somewhat less than the difference in energy intake. The highest contribution for adults comes from apples, followed by grapes and tomatoes. For young children, again the contribution from apples dominates strongly, followed by grapes and some vegetables (tomatoes, Brassicas, carrots). Compared to the ADI of 3 µg/kg bw/d the average TMDI of the 1-4 year old boys is a factor 18 higher than the ADI. When the ADI would be lowered by a factor 10, this figure becomes 180 times the ADI. The ADI for carbaryl is very recent (1996) and has a high uncertainty factor (ca 500) to the probably lowest animal NOAEL, in dogs, to account for indications of developmental toxicity and carcinogenicity

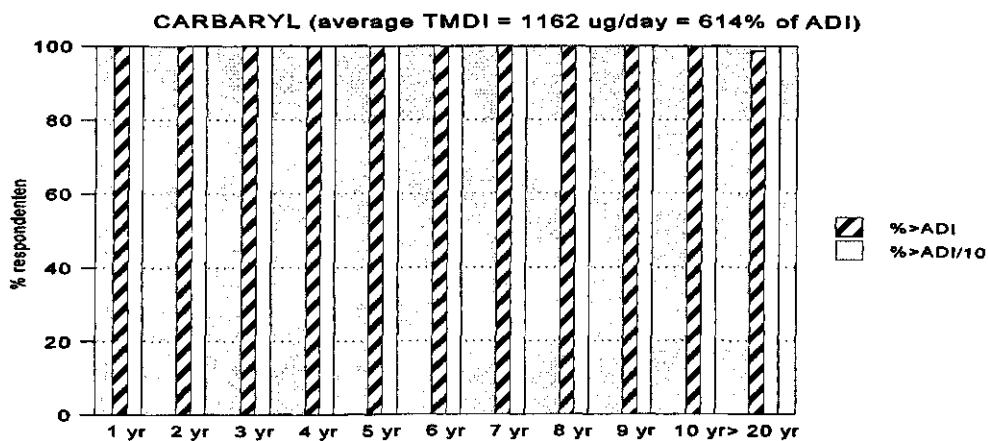


Figure 8. Percentage of subjects with a TMDI exceeding the ADI of lowered ADI, for different age-groups.

Fenvalerate

Figure 9 shows the results of the NTMDI-calculation expressed as percentage of calculated ADI-exceedings. The highest average fenvalerate intake is found in the group 1-4 year old boys, with 12.9 µg/kg bw/d. Compared with the calculated average intake of the DNFCs-population of 4.7 µg/kg bw/d, that is a factor 2.7 higher, comparable to the difference in energy intake. The highest contribution for adults comes from apples, followed by grapes. For young children, apples are again very dominant, followed by milk, grapes, tomatoes and cauliflower. Compared to the ADI of 20 µg/kg bw/d the average TMDI of the 1-4 year old boys is a factor 0.6 of the ADI. When the ADI would be lowered by a factor 10, this figure becomes 6 times the ADI.

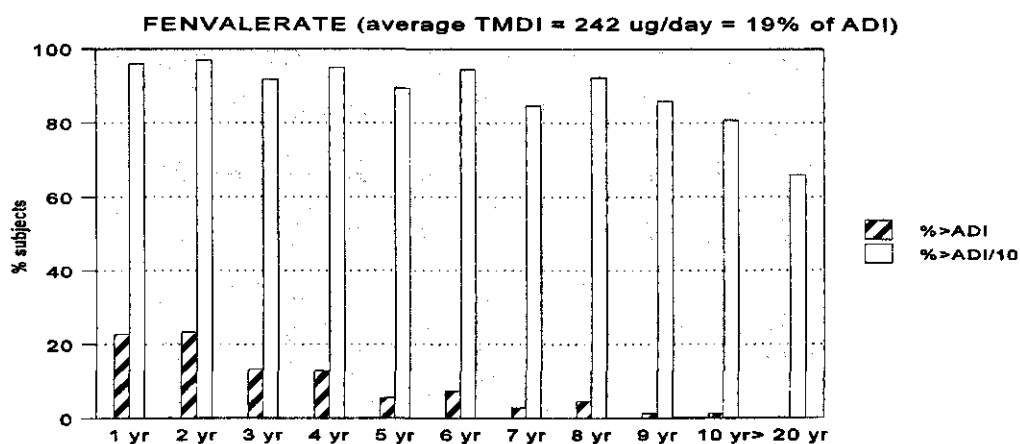


Figure 9. Percentage of subjects with a TMDI exceeding the ADI or lowered ADI, for different age-groups.

4 DISCUSSION OF THE RISK ANALYSIS IN RELATION TO CHILDREN

4.1 Discussion of issues and options regarding enhanced risk assessment

Risk assessment consists of hazard assessment and exposure assessment, which have to be combined to be able to judge the risks involved with using the pesticide.

It will have become evident that appropriate risk assessment should take account of both the specific vulnerability of children, implying a possibly increased hazard, and of the relevant aspects of the potential acute, semichronic and chronic consumption patterns of children and of the resulting potential exposure.

It is evident that the exposure assessment can be improved by taking the consumption data of children into account. The average consumption of age groups is fairly well known by means of the DNFCs. Further research will however be necessary to obtain more reliable consumption figures for infants less than 1 year and for semichronic consumption patterns of subgroups. Further discussion will probably be needed about how high consumption figures that are to be used in exposure assessment should be defined; maximum figures obtained in food consumption surveys can be extreme and obviously are not very reliable.

It is logical that exposure data should be adequately matched with the appropriate toxicological advice that is available. When an ARfD is established, taking account of the vulnerability of children, this should of course be matched with exposure data taking into account high individual acute consumption patterns and maximum levels of the pesticide that can be expected (including unit-to-unit variation). Further research is necessary to be able to perform these estimations in a reasonably realistic way. The investigation of realistic large portion consumptions is essential for the estimation of acute intake.

There is generally consensus that the ADI should also be valid for children. There is still a degree of uncertainty however, whether this only should be matched with chronic consumption patterns over a lifetime, or if semichronic exposures (e.g. consumption patterns during childhood phases, seasonal variations etc.) also have to be taken into account. Many toxicologists seem to be of the opinion that it is the average exposure over a lifetime that matters, not the semichronic higher exposure that can occur during childhood. The Scientific Committee for Food of the EU however states (1997) that the relatively higher consumption of some food items by children should clearly be considered in the risk assessment. Another question is whether long-term consumption patterns of subgroups within the population or individual chronic consumption habits have to be matched with a very general criterion as the ADI. The international guidelines about predicting dietary intake of pesticide residues (WHO, 1989, 1996) are not very clear about this issue. The decision whether subgroups of the population

should be taken into account in the risk analysis is left to countries and international guidance regarding this matter is lacking. Some countries have incorporated the consumption patterns of high consumers, respectively of children, into their risk evaluation procedure. The international (WHO) evaluations of predicted dietary intake of pesticide residues confine themselves to the evaluation of average regional food consumption figures, but this choice at least partly seems to be based on the fact that these figures (based on Food Balance Sheets) are the only international consumption data available.

For a recently established ADI that can be considered to be also suitable for children, because of the adequate data base and acknowledging the recent insights about the vulnerability of children, it will probably be appropriate to take the high semichronic consumption figures of children into account in the exposure assessment. Still, the question remains whether the possibility of exceeding the ADI for a short (but important!) period in life should be seen as an appreciable risk. Renwick and Walker (1993) argue that short excursions above the ADI can be seen as non-significant and propose models for calculating this type of allowance, in relation to the information on which the NOEL was based and the steepness of the dose-response relation. The possible use of categorical regression of toxicity data for the assessment of the real risks involved, when a toxicological reference dose is exceeded, was demonstrated by Dourson et al. (1997) in a case study on the acute risks of aldicarb and the establishment of the EPA-RfD. It is desirable that further toxicological advice is sought about this issue. The question whether and how far exceeding the ADI or the ARfD should be seen as unacceptable is a matter of risk management.

It seems unlikely that enhanced risk assessment procedures, taking account of the exposure of children, would also be fully justified for "old" ADIs that were established based on information that now might be seen as inadequate. Preliminary calculation of potential exposures could however be used to screen for the priority of re-evaluations.

It is concluded that at present it is not yet possible to reach a final conclusion about the exact procedure that should be applied for taking the vulnerability and the exposure of children into account in the risk assessment. Also the appropriateness of applying the ADI or the ARfD with its uncertainty factors to children and to non-average or even extreme consumers may need some further debate among toxicologists and risk management officials. It is obvious that on one side sufficient health protection must be provided to everybody and that uncertainty factors are an essential element in this approach; on the other hand the balance might be lost in relation to the way of dealing with other (food-borne) risks when in the pesticide residues sector a number of uncertainty factors and high risk assumptions would be piled up together.

As long as there are many uncertainties involved with the risk assessment regarding the issue of the greater risks for children, it seems appropriate to wait regarding far-reaching measures and to give priority to further investigating the possible effects on the present risk assessment procedure and the extent of the risks involved. Until now no indications were found that the risks are so large that immediate action has to be taken regarding changes in the risk assessment. Maintaining a prudent approach regarding the level of health protection is clearly necessary, however.

The enhanced incorporation of the susceptibility of children and the dietary intake of children, together with the information on unit-to-unit variation of residue contents, may pose serious problems to the present system of risk management regarding pesticide residues.

When the ADI would have to be lowered, e.g. by a factor 10 (probably the maximum factor necessary), this alone would have a big effect on the risk assessment results and would probably lead to the theoretical possibility of exceeding the ADI for many pesticides. When the diet of children would fully be taken into account in the exposure assessment, already the higher consumption figures on a body weight basis may result in a factor 2-4 higher exposure than that of the average population. The specific consumption patterns of children, implying a relatively higher intake of a number of foods, especially regarding milk, some fruits and vegetables, can add an additional factor to the exposure to pesticide residues.

An option was proposed by Schilter et al (1996), to lower MRLs for foods destined for children. Large companies producing baby foods already apply internal standards that are more strict than the officially allowed MRLs (Beech-Nut, 1997; Gerber, 1995). Some countries have installed a general zero tolerance level (as 0.01 mg/kg) for pesticide residues in baby foods and/or foods for dietetic purposes. As a general principle, the idea to produce foods without (significant) residues for children seems sympathetic and justified in the light of the discussion about the vulnerability of children. It is an option which can count on a lot of public support and on active vigilance by consumer groups (e.g. PANUPS, 1995). Residues found in baby food are often subject to criticism by consumer organisations (EWG, 1996a), even though they are well below official safety standards. Specific low MRLs for foods destined for infants and young children are also being discussed in the EU. When the Scientific Committee for Food was recently (1997) asked to advise the Commission as to whether a MRL of 0.01 mg/kg in these dietetic foods would be adequate to protect this segment of the population, the question did however not involve whether such an approach is really necessary to protect the health of children. The SCF was of the opinion that the relatively higher consumption of specific foods by children was not always taken into consideration in the risk assessment and in the establishment of MRLs. An obvious disadvantage of integrating specific standards for dietetic foods in a regulatory approach is that foods that are produced according to GAP and have been treated with approved uses of

pesticides and normally are on the market and that are prepared at home for the child, would often not concur with these special low tolerances.

The results of the case studies show that the calculated average exposure (NTMDI) of the highest scoring group of children (mostly the 1-4 year boys, sometimes the 1-4 year old girls) to these pesticide residues was between 2.5 and 2.7 times higher than that of the whole DNFCs-population. This implies that the calculated possibility of exceeding the ADI is higher for children than for adults. The average calculated intake of the 1-4 year olds exceeds in 3 of the 4 cases the ADI, whereas in 2 of these 3 cases the ADI was not exceeded for the average DNFCs-population. Only carbaryl shows high exceedings in all age groups, and the ADI of fenvalerate is not exceeded by the average of the 1-4 year olds. It will be clear that when it is assumed that a child-adjusted ADI would be 10 times lower, the calculated exposure becomes 10 times higher in relation to this new ADI and then for all compounds the ADI is exceeded for most of the children.

It should be borne in mind that the NTMDI-calculation which has been performed here is a gross overestimation of the real chronic exposure and should not be regarded as realistic. Because the ADI for most compounds that were evaluated here is fairly recent, it also in fact is unlikely that a 10 times lower ADI would be needed to accommodate the specific vulnerability of children. The calculation has been performed however to show the effect of such a change. Because for carbaryl the factor by which the ADI is exceeded is so high, a more realistic estimation of the exposure to this compound deserves priority.

Because the diet of children is more simple and less varied than that of adults, the results of a NTMDI-calculation probably tend to resemble more or less the outcome of an acute intake estimation, in which MRLs are used. Therefore the conclusion that the ADI is exceeded for children in a calculation of the NTMDI should not only lead to investigating the chronic exposure in a more realistic calculation model, but also to giving attention to an estimation of the potential acute exposure of especially children.

It is to be expected that the 1 year olds as a group show a somewhat higher exposure than the 1-4 year olds taken together, because their average diet is somewhat higher on the basis of consumption per kg body weight. Also, higher exposures are to be expected from subgroups of these age groups with higher intakes of specific food commodities. Further insight in these chronic and semichronic consumption patterns may probably come forward from food frequency enquiries that are being performed in the 1997/1998 DNFCs. The infants younger than 1 year were not involved in the evaluation because their consumption was not available in the DNFCs. All these aspects deserve further study which could not be included in the present investigation.

Conclusions

The conclusion of the literature review about the health aspects of children related to pesticide residues is that the debate about the issue is still dominated by the USA, but that also existing legislation in Europe about baby foods is relevant for the discussion. Baby food producing companies are active in incorporating more strict standards in their products. Generally, no ground for immediate government action for health protection purposes was found, but on the other hand the arguments used are serious enough to conclude that further specific evaluation of all aspects and investigation of possible improvements in the risk assessment and risk management procedures is desirable. It is to be expected that the discussion also in Europe and in Codex will be intensified as results come available of investigations about exposure assessment and subsequent risk assessment for children. Also the results obtained with the calculations in this study indicate that the matter is serious enough to warrant further investigations and evaluation of management options.

Potentially, the risks of pesticide residues for children are considerably larger than for adults, for whom the present risk analysis generally seems adequate (even though specific consumption patterns may warrant some further evaluation). The magnitude of the higher risks for children in relation to adults can on the basis of this study be assumed to be mostly ca 2-4 times higher when only exposure is taken into account; this may have been magnified by a factor of at most 10 when also a higher susceptibility of children is assumed.

In this study, the possibility of the present ADI being exceeded was found to exist for most young children in 3 of the 4 cases for which NTMDI calculations were performed, whereas this was the case only for 1 compound for the average of the whole population. When a 10 times lower child-adjusted ADI is assumed, all compounds exceed the ADI for most of the children. It must be borne in mind however that the NTMDI-calculation results in a gross overestimation of the real intake and there is no firm scientific basis for lowering the ADI for children as a general approach. Specific conclusions can only be drawn on a case by case basis and after careful evaluation of the best possible hazard and exposure data.

It is not very likely that these larger potential risks involve that children have suffered adverse effects from pesticide residues that were approved under the present risk analysis procedures, because of the large uncertainty factors that are used to ensure safety. The 1993 JMPR mentions that there is no evidence that such residues present a risk to human health in any population group.

Recommendations

Further investigation is necessary of the possibly greater susceptibility of children in all phases of their development to adverse effects of chemicals, and to pesticide residues in particular, and of the extent of the risks involved.

Further evaluation is desirable of the necessary toxicological database to assess the risks of pesticide residues for children.

An investigation is desirable of the priorities in assessing the real risks of pesticide residues for children, e.g. by screening the potential intake by children compared to the ADI.

Further details are required about the consumption patterns of infants aged less than 1 year, and about non-average semichronic consumption patterns of young children.

Further elaborated studies are desirable about the best possible estimation of the (semi-)chronic intake for especially children of a number of priority pesticides where the NTMDI for children exceeds the ADI.

It is desirable to perform studies aimed at more precisely assessing national short term consumption patterns of especially children and to investigate the possible extent of acute exposures for a number of priority compounds (a.o. aldicarb).

Further preliminary inventarisation is desired of risk management options and strategies related to the risk analysis of children regarding pesticide residues.

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GLOSSARY OF ABBREVIATIONS

Terms designated with an * are further explained in the Annex to this report

ADI*	Acceptable Daily Intake
ARfD*	Acute Reference Dose (short term intake that is considered safe)
CAC	Codex Alimentarius Commission
DNFCS	Dutch National Food Consumption Survey
EPA	Environmental Protection Agency (of the USA)
EU	European Union
GAP*	Good Agricultural Practice
FAO	Food and Agriculture Organization (of the United Nations)
FDA	Food and Drug Administration (of the USA)
FQPA	Food Quality Protection Act
IEDI*	International Estimated Daily Intake
JMPR	Joint Meeting of Experts on Pesticide Residues
KAP	Programme for the Quality of Agricultural Products (Kwaliteitsprogramma Agrarische Produkten)
LD ₅₀	Lethal Dose for 50 % of the test animals of one species
LOD	Limit of Determination (not to be confounded with the Limit of Detection, which is lower)
LOQ	Limit of Quantitation (essentially the same as the Limit of Determination)
LOEL	Lowest Observed Effect Level
MRL*	Maximum Residue Limit
NO(A)EL*	No Observed (Adverse) Effect Level
NRC	National Research Council (of the USA)
NTMDI*	National Theoretical Maximum Daily Intake
OECD	Organization for Economic Cooperation and Development
SCF	Scientific Committee for Food (of the European Union)
STMR*	Supervised Trials Median Residue
TMDI*	Theoretical Maximum Daily Intake (international assessment, for regional or cultural diets in the world)
WHO	World Health Organization (of the United Nations)
WTO	World Trade Organization

1 General principles and regulatory practices

The policy of the Netherlands regarding pesticide use is already for many years based on the principle that the use of a substance or a preparation as a pesticide is only allowed when based on adequate scientific evidence it is shown that the pesticide is effective for its intended use and (a.o.) does not have a harmful effect on the health of humans and animals, both directly or indirectly. The criteria by which compliance with the Pesticide Law is checked, are harmonized in the EU in the framework of Directive 91/414 and these uniform principles are incorporated in the Dutch law since 1995. The interpretation of the criteria is also harmonized to a certain extent, but there is room for discussion and the possibility of taking on board new scientific views that emerge on specific issues. Therefore the discussion on the special vulnerability of children and the question if this is sufficiently taken into account in the present risk management of pesticide residues is relevant and could lead to a different interpretation of risks and to different risk management decisions and thus have an effect of the decisions regarding pesticide use.

The policy regarding pesticide residues in the Netherlands is that maximum levels in foodstuffs are established in the Residue Regulation, in the framework of the Pesticide Law. In principle all pesticides that are allowed for use in the Netherlands are completely covered by appropriate maximum levels according to their approved use (Van Eck and Dornseiffen, 1995). For the sake of international harmonisation also maximum levels covering approved uses in other countries are adopted, as far as they are established in EC-Directives, or in Codex recommendations (as far as they were considered acceptable), or as import tolerances, on the request of importers or exporters. All commodities that are not covered by these mentioned maximum levels, for all pesticides mentioned in the Residue Regulation, are consigned a zero tolerance, at the level of the analytical limit of quantitation. The residue levels and the adherence to maximum limits are controlled by the Health Inspectorate and by private institutions and companies that are responsible for the quality of foodstuffs.

2 Present risk analysis system for pesticide residues

2.1 Risk analysis

The risk analysis system and the definitions as developed by Codex is largely followed in the Netherlands. The main principles are mentioned shortly here.

Risk analysis is the process of performing a risk assessment, followed by appropriate risk management and assuring adequate risk communication.

Risk assessment is the scientific evaluation of the probability of occurrence of known or potential adverse health effects resulting from human exposure to foodborne hazards. This evaluation consists

of the following steps: (i) hazard identification, (ii) hazard characterisation, (iii) exposure assessment, and (iv) risk characterisation.

Risk management is the process of weighing policy alternatives in the light of the results of risk assessment and, if required, selecting and implementing appropriate control options.

Risk communication is the interactive exchange of information and opinions concerning risks among risk assessors, risk managers, and other interested parties.

2.2 Hazard characterisation

First the hazard must be identified, by gaining information on the known or potential adverse health effects produced by the substance or agent to which man can be exposed. Hazard characterisation is then the qualitative and/or quantitative evaluation of the nature of the adverse effects, implying that for chemical agents a dose-response assessment should be performed.

For adequate hazard characterisation, a number of toxicity tests have to be performed, usually by oral administration of the substance to laboratory strains of several species of animals in a specified test protocol.

The general principle of the toxicological evaluation is that insight is necessary in the nature of the toxicity of the compound and that a dosage level of the pesticide should be established which does not imply a risk for those that may be exposed to the pesticide, either by operational or incidental contact or by intake of residues via food and water consumption. The toxicological evaluation as it is now performed leads to the establishment of a NOEL or a NOAEL (when the data base permits such a conclusion), at the lowest level found not to have an effect on animals, or no adverse effect. When a substance is shown to have carcinogenic effects, and no threshold level without a possible effect can be established, a risk estimation approach will be necessary to evaluate possible effects on public health. For pesticides in the EU generally a no risk approach for consumers is aimed for, therefore a no (adverse) effect level should be and is the basis for the toxicological advice. (A slightly different approach is the benchmark dose, in discussion in the EPA).

The NOEL or NOAEL is used to derive a level considered safe for humans, by applying appropriate safety factors (also termed uncertainty factors) to account for the possibility that humans are more sensitive than animals to that chemical and to account for the variation in sensitivity between the population. Current use is to apply a factor 10 for each risk possibility, leading to a factor 100 to derive this safe intake level from the NO(A)EL. Additional safety (uncertainty) factors may be used when the data base was not completely satisfactory or when adverse effects have been found that are thought to imply the necessity of a more cautionary approach (e.g. teratological or other developmental effects). The WHO and its expert bodies and European countries use the term ADI for the final

toxicological advice about the acceptable daily intake of the chemical that has been evaluated; in the USA the term RfD (Reference Dose) is used.

The ADI is meant to be applicable to lifetime exposure and is expressed as substance dose per kg body weight. It is a crucial parameter in evaluating the risk of the chronic intake of pesticides and in establishing MRLs that may be considered safe.

Recently, more insight in the nature of the acute toxicity of some compounds and in the possible occurrence of high residue levels in products eaten in one portion or meal, has led to the development of a parameter for acute toxicity, the acute reference dose (ARfD), which can be used for the evaluation of acute risks of pesticide residues.

2.3 Development of maximum residue levels

Pesticide Residue means any specified substance in food, agricultural commodities or animal feed, resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products and impurities considered to be of toxicological significance. A Maximum Residue Limit (MRL) is the maximum concentration of a pesticide residue (expressed as mg/kg), (recommended to be) legally permitted in or on food commodities and animal feeds. MRLs are based on GAP data and foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable. The definition of GAP (Good Agricultural Practice) includes the nationally authorised safe uses of pesticides under actual conditions necessary for effective and reliable pest control. It encompasses the whole range of pesticide applications up to the highest authorised use, applied in a manner which leaves a residue which is the smallest amount practicable. The method that is used world-wide for the establishment of MRLs for pesticide residues is that MRLs are developed by reviewing residue analysis results of products sampled from supervised trials with pesticides used at a dose level which is (intended to be) legally approved and which are considered to represent effective pest control practices. The highest analysis results of the highest authorised national dose level are used to propose a MRL. An MRL is thus a rounded-off figure that is slightly higher than the highest reliable residue level that can be expected to result from authorised use of a pesticide; this assures that pesticides applied according to GAP will always lead to a product that meets the MRL. It also means that pesticide residues occurring in products will usually be much lower than the MRL. A higher residue than the MRL is possible when GAP was not followed (e.g. by applying a higher dosage than is allowed, or by a shorter pre-harvest interval than was advised). In small individual samples, residues can sometimes be higher than the MRL due to the variability of the application and the dissipation of the pesticide; that variation is less reflected in the composite samples used for MRL establishment and control.

The residue definition applied in MRLs (recommended to be) established in food legislation is usually shaped in such a way that MRLs can be regularly controlled by routine laboratory analysis. This can

imply that metabolites or reaction products that are important for the exposure assessment are not always included in the residue definition. When this is the case, a different residue definition or correction factors to the MRL may have to be used in the exposure evaluation.

2.4 Judging the acceptability of MRLs by exposure assessment

The description of the method used for developing MRLs does not contain a toxicological element as such; therefore the safety of (proposed) MRLs must be checked by applying a suitable risk assessment method. In the presently used risk analysis system for pesticides, the necessary exposure assessment is performed in a tiered way in order to avoid undue effort. The principle consists of applying an intake calculation model based on the proposed MRLs for foods and their respective consumption figures; the resulting calculated exposure is compared to the appropriate toxicological parameter (ADI or ARfD, where applicable).

The guiding principle of risk management is that the ADI or ARfD should not be exceeded. An important issue is how it should be established that MRLs can be considered safe for consumption. The calculation method has been mentioned already and is described more fully below. A method which is used to check the outcome in practice is the analysis of residues in the total diet. The results obtained in this way are always very reassuring, because the residue levels are shown to amount to an intake which is a few percent of the ADI, or less. This investigation is only very rarely directed towards the exposure of children however. A disadvantage of this approach is also that it is unsuitable to predict the intake that can be expected when new pesticide uses are put forward for approval or when new import tolerances are proposed for acceptance; for these situations calculation of the potential exposure is the only possibility.

Because in principle it is considered necessary to judge the acceptability of (a complete set of) MRLs before a pesticide can be permitted to be used, or before import tolerances can be established, the desirability of a harmonised approach regarding calculated intake estimations for pesticide residues has become apparent in the last decades. The WHO issued guidelines for this purpose in 1989 and is currently working on a revision of these guidelines (FAO, 1996). The system includes a tiered approach, in which increasingly more sophisticated estimations models are used to assess the potential intake in relation to proposed MRLs. The first tier consists of a theoretical maximum daily intake (TMDI) calculation, using the MRLs as such. The second tier is applied when the TMDI exceeds the ADI and is aimed at a more realistic intake approximation (IEDI) by using appropriate reduction factors in relation to the MRL. A major reduction effect already occurs by calculating with the STMR (the median residue found in the supervised trials that formed the basis for the MRL). Other important factors are the effect of peeling and processing of the product.

The consumption figures used in the exposure assessment are average regional diets, when an international evaluation is performed. Countries are free to choose their own system for health protection of their population and therefore there are varying system is used in applying national diets in these exposure estimations. Sometimes these include using the diet of children, or of other subgroups, or defined percentile values within the consumption patterns of the population.

When a ARfD has been established, a different exposure estimation has to be made. In that case, individual large portion sizes and daily intakes are relevant, and regarding the residue level the MRL has to be used (or even a higher figure, when there is evidence of large unit-to-unit variation in the product).

Some pesticides show the potential to exceed the ADI (or the ARfD) in the international or national exposure calculation and therefore the safety of these MRLs may be questioned. The discussion in Codex about the risk management policy to be applied regarding Codex MRLs that are subject to a debate about their safety has recently led to a (temporary) procedural solution by making a clear distinction between the international approach, and the national approach, which can go a step further in this theoretical intake estimation model (CAC, 1997). One of the main differences between the national and the international approach will be the use of the national diet in the exposure assessment. Especially when consumption patterns of subgroups, such as children, are included in the evaluation, the results can be rather different from the international evaluation and therefore conclusions regarding the acceptability of MRLs could also be different. This implies that countries that do not accept specific residues in imported products may have to defend their case to a WTO-panel and will then have to use health protection arguments based on national exposure calculations.

The Netherlands, in the wake of the debate about the acceptability of MRLs and in relation to the increasing obligations of international harmonisation, has paid increasing attention in the last years to developing more refined methods of intake estimation in relation to MRL establishment. Research has been directed to establish a link between the national data base of food consumption figures (based on foods as eaten) and the MRLs, which are set for primary agricultural commodities. Based on a conversion model, a data base is now available on the national diet, expressed in primary agricultural commodities (Dooren-Flipsen et al, 1996). This allows national exposure calculations based on MRLs or monitoring data. At present NTMDI calculations are routinely made for new registration requests. Further refinements will be necessary however, for a full incorporation of newly proposed international risk estimation methodology into the Dutch regulatory system.

The discussion about the special vulnerability of children may also require further elaborated risk assessment and risk management actions. Some other important new developments that will need further attention in the risk analysis of residues in food are the establishment by the JMPR of advice for

acutely toxic substances, and the growing evidence of large unit-to-unit variation in pesticide residues, implying that acute doses could be higher than the MRL suggests (because the MRL is based on composite samples that are mixed to be representative for a lot).