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## Executive summary

Health Council of the Netherlands. *Pesticides in food: assessing the risk to children*. The Hague: Health Council of the Netherlands, 2004; publication no. 2004/11.

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### Background to this advisory report

Pesticides are widely-used chemical preparations: they protect agricultural crops against disease and infestation, they remove weeds from pavements, and they combat vermin in and around homes. These products may also be harmful to other organisms, including humans. That is why they are only allowed onto the market after extensive safety assessment. In the Netherlands, the Board for the Authorisation of Pesticides (CTB) is responsible for making that assessment. This agency assesses issues such as whether sprayed agricultural produce is safe for consumers. To do so, it uses a scientific, internationally accepted method. In 1996, the United States revised several aspects of the usual approach, with a view to providing better protection for children. In Europe, the authorities have also started to reappraise their approval procedures for pesticides. As a precautionary step, standards for pesticides in baby food and baby formula have been tightened-up. In the Netherlands, and indeed throughout the world, the issue has given rise to an ongoing debate about whether the usual approval procedure would actually cause children to be harmed by sprayed food.

Against this background, the Minister of Health, Welfare and Sports, also on behalf of the former State Secretary of Agriculture, Nature Management and Fisheries submitted the following questions to the Health Council:

- Are children more vulnerable to xenobiotic compounds in general and to pesticides in particular?

- What does this mean for the derivation of safe levels for chronic and short (generally a single) exposure to these substances?
- How can the risk assessment take into account the fact that levels of child exposure to pesticides are different from average exposure levels because children have different patterns of food consumption?

The Committee that drew up the advisory report has taken into consideration all the phases of childhood, from embryo to adolescent. It first provides a description of how exposure and response to pesticides varies between children and adults. It then discusses the current risk assessment procedure for these substances. Finally, it deals with the question of whether that procedure is sufficiently well tailored to children. The advisory report concludes with a series of recommendations.

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### **Exposure of children to pesticides**

The food consumption patterns of children are different from those of adults. The younger the child, the greater the difference. After birth, children are breast-fed or bottle-fed. After four to six months, weaning starts and, from about ten months onwards, children gradually start eating the same as the rest of the family. Per kilogram of body weight, children aged from one to six consume greater amounts of certain foods than adults. The foods in question are milk and dairy products, fruit juices and cordials, fruit and vegetables, cereal products, sweets, and sweet sandwich fillings. Therefore, per kilogram of body weight, they are more exposed than adults to the pesticides in these products.

Young children crawl a lot. They also often put their hands and all sorts of objects in their mouths. This behaviour can similarly result in higher exposure through the oral pathway. Per kilogram of body weight, children also have more body surface area and breathe in more air than adults. This results, relatively speaking, in a higher exposure to substances via the skin and the respiratory system.

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### **Processing of substances by the body of a child (toxicokinetics)**

Children are physiologically different from adults. The younger the child, the greater the difference. This affects the uptake of substances in the body, the distribution through tissue, metabolism by enzymes and excretion from the body.

Before birth, children are protected from the outside world by their mother's bodies. However, many xenobiotic compounds can pass through the barriers between the mother and the child. After birth, the gastrointestinal tract constitutes an important uptake route. However, at birth the gastrointestinal tract has not yet reached full

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maturity. As a result, neonates absorb some substances better than adults, and actually absorb others less well.

The way substances spread through the body also depends on age. In particular, substances which dissolve well in water spread to a relatively larger volume in babies' bodies than in adults. From the circulatory system, they also penetrate more easily into tissues and organs, including the brain.

In foetuses and in neonates, the ability to metabolise chemical substances with enzymes is still limited. As a result, the detoxification and excretion of poisonous substances take place slowly. On the other hand, the lower level of enzyme activity provides protection against substances that are metabolised by enzymes into more harmful substances. In addition, the kidneys and the liver do not yet function at adult levels in neonates, so excretion is slower.

All the toxicokinetic differences between children and adults referred to here largely disappear during the first year of life. Older children may even surpass adults in terms of their ability to metabolise substances with enzymes and then excrete them. This is because children have a higher metabolic rate.

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### **Effect of substances on the body of a child (toxicodynamics)**

While chemical substances may produce the same types of effects in adults and children, these can occur at different exposure levels. In addition, substances can result in effects that are unique to children, and that are associated with adverse effects on the development of organs or organ systems. During development, there are periods in which organs can be particularly vulnerable to the influence of chemical substances. These periods are known as windows of vulnerability. In recent years, there has been a growing awareness that disturbances of the maturation of organs may ultimately lead to impaired functioning, even if the organs are apparently healthy. These functional shortcomings sometimes only emerge in adulthood.

Animal trials have shown that some pesticides can affect the development of organs and organ systems. Young laboratory animals can suffer damage to the brain, reproductive organs and immune systems after exposure to doses of pesticides that do not induce any perceptible harm in adult animals. In adult animals, low doses usually only produce effects after long-term exposure. However, in young animals, short or even a single exposure can be enough to produce an effect. In so far as the same effects have been studied and found in both adult and young animals, they are often more severe and longer-lasting in the latter.

There have been no studies to determine whether low levels of exposure to pesticides through food can have similar effects on human development. More is known about the effect of certain pollutants (such as lead, dioxins, and PCBs), certain

medicines (DES, thalidomide) and natural stimulants (alcohol). These can adversely affect the development of children, particularly unborn children, at levels of exposure that are not harmful to adults.

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### **The current appraisal procedure for food safety**

The Board for the Authorisation of Pesticides (CTB) assesses the risks of long-term exposure to pesticides through food. To do so, it determines the amount of the pesticide in question that consumers can ingest each day, throughout their lifetime, without running an appreciable risk. This Acceptable Daily Intake (ADI) is expressed as milligrams per kilogram of body weight per day. The assessment is based on data from animal trials, which the manufacturer is required to provide. The CTB uses this data to derive the highest exposure level at which no harmful effects are found in laboratory animals. The ADI is then calculated by applying uncertainty factors that compensate for the differences between animals and humans, and for differences between people. Current thinking is that, in the case of substances that can damage genetic material and thereby cause cancer, it is impossible to determine an exposure level at which no effects occur. Substances of this kind do not qualify for approval.

The CTB also makes an initial, rough estimate of the amount of pesticide that consumers might ingest with their food. For safety's sake, the worst-case scenario is assumed here. In other words, high levels of consumption and high levels of pesticides. Consumption by children aged from one to six is dealt with separately.

The CTB then compares the estimated level of exposure to the level that is considered safe. If exposure, both in the general population and among children aged between one and six, remains below the ADI, the CTB will consider the pesticide to be acceptable. If the calculated exposure is higher, the CTB will conduct a more refined calculation based more on the actual circumstances, in which it takes into account, for example, the consequences for exposure of how food is prepared (washing, peeling, cooking). If the ADI is still exceeded, approval will only be possible after changes to the pesticide's instructions for use, leading to a reduction of exposure to below the permissible standard.

For a number of years now, it has been clear that the level of pesticides in individual products – for example, a single apple – is sometimes higher than was assumed on the basis of analyses of pooled samples. This is particularly important in the case of pesticides with a high acute toxicity. In order to protect consumers against peak exposures, the Acute Reference Dose (ARfD) is determined for these substances as well as the ADI. This is the amount of a particular pesticide that consumers can ingest during a single meal or a single day without appreciable risk. Here also, the CTB makes a separate estimate of the exposure for children aged between one and six, in addition to

intake by the general population. If this initial worst-case calculation indicates that the ARfD may be exceeded, a more refined, more practice-oriented estimate will follow. If the ARfD is still being exceeded, adjustments will be required to the instructions for using the pesticide.

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## **Conclusions about tailoring the current safety assessment procedure to children**

The Committee of the Health Council that drew up this advisory report concludes that children can be both more and less vulnerable to substances than adults. Vulnerability can vary according to the substance and depends on the stage of development of the child in question. Current toxicological research therefore includes all developmental stages of organisms. However, this research is neither sufficiently profound nor broad enough in terms of design to identify every single effect on the main organs and organ systems in developing organisms. In particular, effects on the development of the nervous system and the immune system may remain unnoticed. This may also apply to effects resulting from endocrine disruption. Changes which are most likely to remain unnoticed are those resulting from exposure during development that only emerge in later life.

Information about the influence of pesticides on the development of the nervous system, the immune system and endocrine-regulated processes is important for the derivation of safe levels for both short and chronic exposure to pesticides. It is unclear to what extent the lack of this relevant data about development toxicity is offset by the traditional uncertainty factor for variations in vulnerability between individuals. This means that it is also unclear whether the current calculations of safe intake levels always provide adequate protection for children, including unborn children, in periods of heightened vulnerability during the course of their development. In some cases, protection of the foetus may require stricter standards for acute exposure (ARfDs) than are required for the protection of other age groups. The question of whether one wishes to derive separate, less stringent standards for the latter is a policy issue. The Committee finds that the current risk assessment procedure correctly takes into account the specific consumption patterns of children aged between one and six.

At present, there are no concrete indications of genuine adverse effects on children's development caused by the presence of pesticide traces in food. However, this matter requires further research. Furthermore, effects involving aspects such as behaviour, learning ability, motor skills, immunity or fertility are difficult to identify. Research has shown that some substances can have an adverse effect on the development of children. Examples are PCBs, dioxins and lead.

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## Recommendations of the Committee

The number of toxicological studies that manufacturers are required to conduct as standard need not be increased. Nevertheless, improvements are required to existing research protocols. In particular, studies of reproduction toxicity involving several generations of laboratory animals should be designed on broader lines, to allow for the identification of any effects on the development of the nervous system, immune system and endocrine-regulated processes of development. If this standard research yields an indication that there may be an adverse effect on the development of organisms, there should be follow-up research into the specific problem. In effect, this is already a requirement, but there are still no validated research methods available for a range of follow-up studies. There are international initiatives in progress with a view to drawing up research protocols. The committee recommends Dutch support for these activities.

As long as the current research procedures do not achieve full success in determining possible harm to development, data about the toxicity of pesticides is, in effect, incomplete. The Committee believes that the best way to tackle this problem is to have experts assess each pesticide individually. If, on the basis of all available toxicological data and in the absence of adequate research or follow-up research, there is reasonable cause for supposing that developing organisms are more vulnerable than adult organisms, the Committee believes that an additional uncertainty factor, in addition to the factors traditionally used, is appropriate when calculating the ARfD and the ADI. In many cases, it will not be feasible to supply scientific justification for the size of any additional uncertainty factor. Where this is the case, a default value of 10 could be chosen. This value is traditionally used to account for the absence of key data. Alternatively, values 3 or 10 can be chosen. These are used in the United States. As soon as the missing data becomes available, it will be necessary to determine whether it justifies a change to the ADI or ARfD. International collaboration is indispensable here, in order to prevent different countries setting different ADIs and ARfDs.

The United States is currently reassessing all pesticides in terms of their safety for children. In the case of many pesticides, the additional uncertainty factor assigned beforehand to all pesticides for the protection of children was removed after completion of this reassessment. However, the additional factor was retained for a few pesticides. In the Netherlands and in Europe as a whole, priority should be given to a reassessment of these substances to determine their harmfulness to developing organisms. The same applies to pesticides where there is a small margin between the calculated or measured exposure and the level of exposure considered safe.

Human food consumption patterns change over the course of time. This is also true of children. The Committee therefore considers it to be very important for future food

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consumption surveys to obtain information about children. It recommends including consumption by children aged between six months and one year in the surveys and, where necessary, including them in the risk assessment.

The possibility of simultaneous exposure to several pesticides with a common mechanism of toxicity and of simultaneous exposure to the same compounds from various sources (food, water, domestic uses) merits systematic attention in the risk assessment of individual pesticides. However, appropriate methods are still being developed. The Committee advocates the use of Dutch expertise as support for the international activities in this field.

Pesticides policy, including the way in which the risks associated with the substances are assessed, is increasingly determined by the European Union. The Committee therefore urges the Dutch government to put forward its recommendations for discussion within the European Union (including the European Food Safety Authority), where decisions can be taken at the central level.