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Guidance for assessment of chemical risks for children

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Rapport in het kort

Leidraad voor risicobeoordeling van chemische stoffen voor kinderen

Het RIVM heeft een leidraad geschreven voor de risicobeoordeling van chemische stoffen voor kinderen. In een dergelijke risicobeoordeling wordt de mate waarin een kind wordt blootgesteld aan een bepaalde chemische stof gerelateerd aan de mogelijk schadelijke effecten van deze blootstelling. Er bestaat momenteel veel belangstelling voor risicobeoordeling van chemische stoffen voor kinderen. De beoordelingsmethodes zijn echter nog sterk in ontwikkeling. De leidraad biedt handvatten bij het maken van een risico-evaluatie en wijst risicobeoordelaars op de verschillende aspecten die bij een risicobeoordeling van stoffen voor kinderen kunnen worden betrokken, zoals de specifieke blootstelling en de specifieke gevoeligheid van een kind voor de schadelijke effecten van een chemische stof. Dit zal de consistentie in de risicobeoordelingen bevorderen.
Verder worden voorstellen voor verbetering van risicobeoordelingen van stoffen voor kinderen gedaan. Wanneer deze voorstellen worden doorgevoerd zal dit een aantal gevolgen hebben, bijvoorbeeld dat testrichtlijnen moeten worden aangepast. De mogelijke gevolgen van deze voorstellen worden in het rapport bediscussieerd.

Trefwoorden:
kinderen, chemische stoffen, blootstelling, gezondheid, risicobeoordeling

Abstract

Guidance for assessment of chemical risks for children

Every day humans are exposed to chemicals, either from food and/or non-food sources, such as consumer products. In regulatory toxicology, recent attention has focussed on the possible differences between children and adults with respect to susceptibility and exposure to chemicals. The present RIVM report aims at providing guidance on performing assessments of risks for children. The report discusses child-specific toxicokinetics, toxicodynamics and exposure, and also addresses the adequacy of, and the data gaps in, the present methods of risk assessment. The intention of such research is to make risk assessors aware of the different aspects that should be taken into consideration when performing assessments of chemicals posing risks for children. A variety of toxicological tests in animals has been developed to assess the adverse health effects of chemicals. However, concern has arisen about whether the current test protocols adequately cover potential effects in the early life stages. In this document, the guidance for risk assessors on the strategy to be used when performing risk assessments for children addresses this concern and stimulates consistency in the assessments. Several issues relevant to the risk management of chemicals are discussed as well, accompanied by a number of recommendations for improvements in performing assessments with respect to risks for children.

Key words:
Children; chemicals; exposure; health; risk assessment

Contents

Samenvatting

Mensen worden dagelijks blootgesteld aan chemische stoffen, zowel uit de voeding als uit andere bronnen, zoals consumentenproducten. In de *'regulatory toxicology' (beleidsondersteunende toxicologie)*, is de laatste jaren de aandacht gevestigd op de mogelijke verschillen tussen kinderen en volwassenen met betrekking tot de gevoeligheid voor en blootstelling aan chemische stoffen. De schadelijke effecten van stoffen worden onderzocht in verschillende toxiciteitstesten in dieren. De vraag is echter of de huidige testen de mogelijke effecten van stoffen in de vroege levensfasen kunnen aantonen.
Het huidige document is bedoeld als leidraad voor de risicobeoordeling van stoffen voor kinderen. Het document bediscussiëert de kind-specifieke toxicokinetiek, toxicodynamiek en blootstelling en bespreekt de geschiktheid en de hiaten in de huidige risicobeoordelingsmethodes. Het is bedoeld om risicobeoordelaars te wijzen op de verschillende aspecten die moeten worden betrokken in de risicobeoordeling van een stof voor kinderen. Het document geeft een leidraad aan risicobeoordelaars bij de te volgen strategie bij de risicobeoordeling voor kinderen, en bevordert zodoende de consistentie in de evaluaties. Ook wordt een aantal kwesties die van belang zijn voor het beleid inzake risico's van stoffen bediscussiëerd. Tevens wordt een aantal aanbevelingen gedaan voor verbetering van de risicobeoordeling voor kinderen.

Summary

In regulatory toxicology, recently attention has focussed on the possible differences between children and adults with respect to susceptibility and exposure to chemicals. Concern has been raised whether the current test protocols adequately cover potential effects of chemicals in the early life stages.
The aim of the present document is to provide guidance with respect to risk assessment for children. It is intended to make risk assessors aware of the different aspects that should be taken into consideration when performing a risk assessment of a chemical with respect to children. In the document guidance is provided for risk assessors on the strategy that may be used when a risk assessment for children is performed, thereby stimulating consistency in the evaluations. In addition some issues relevant to the risk management of chemicals are discussed. Furthermore a number of recommendations for improvement of risk assessment for children are made.
Substantially differences in toxicokinetics, toxicodynamics and exposure exist between children and adults. This should be taken into account when performing risk assessment of chemicals. In the present document the child-specific toxicokinetics, toxicodynamics and exposure are discussed, and the adequacy of, and the data gaps in the present methods of risk assessment are addressed.
With respect to toxicokinetics, the risk assessment could be refined by estimating, by the use of PBPK-models, the internal exposure in children and differences in toxicokinetics between children and adults. More research into the development of such PBPK models is needed. In addition, an indication of the differences in toxicokinetics between children and adults can be obtained from toxicokinetics studies using juvenile and adult animals.
The health effects (toxicodynamics) of a chemical are studied in a variety of toxicological tests in animals. However, a number of potentially important toxicological parameters for children are not or only partly investigated in these tests. The investigation of a broader set of toxicological parameters in the multi-generation toxicity test may provide at least part of the information that is lacking at present. Also other studies in juvenile animals could be used to obtain information on possible effects of a chemical in children. Such studies need not to be included in the set of standard toxicity tests, but should performed only when data indicate the need for such a test. It is recommended that further guidance on the use of specific juvenile animal studies in risk characterisation and risk assessment is developed.
Differences between children and adults in external exposure might be due to differences in behaviour, dietary pattern, physiological characteristics or exposure pattern. For risk assessment of children, dietary and non-dietary exposure to a chemical should be estimated for children of different age groups. Dietary exposure can be estimated by the use of the available data on dietary intake of children of different age groups. For non-food sources of chemicals such as consumer products, reasonable worst case estimates of exposure levels of children can be obtained by the use of mathematical consumer exposure models, such as ConsExpo.
It is concluded that risk assessment for children should be performed by experts for all chemicals to which children are exposed, on a case-by-case basis. If, based on the toxicological information, there is a concern that children of a certain age group may be more sensitive to the toxic effect of a chemical, it should be considered whether the default (10x) intraspecies safety factor is sufficient to protect these children. If this is not the case, an additional safety factor should be applied.

1. Introduction

Every day humans are exposed to chemicals, either from food and/or non-food sources, such as consumer products. In the regulatory toxicology there is increased awareness that considerable differences between children and adults in exposure and sensitivity to chemicals may exist. In several reports the consequences this may have on risk assessment of chemicals has been discussed, e.g. by Nielsen et al. [1], and Wolterink et al. [2]. It has been shown that there are sometimes differences in toxicokinetics and toxicodynamics between the developing animal and the adult animal, and for children and adult humans. In addition, the exposure pattern and exposure levels to chemicals may differ between children and adults. Furthermore, it has to be noted that also between children of different ages considerable differences in toxicokinetics, toxicodynamics, and exposure exist. In view of this, it is generally acknowledged that children are a potentially sensitive group in the human population.
Most data on the toxicity of chemicals are obtained from animal studies. For the establishment of a safe exposure level in humans, most organisations (e.g. JMPR, JECFA, EU) consider the 10 x 10 assessment factors (for interspecies and intraspecies variation), applied to the overall No Observed Adverse Effect Level (NOAEL) in animals, sufficient to protect the human population, including sensitive groups such as children, providing that the toxicological data base is considered adequate. A potentially more conservative approach is used by the USA. The US Food Quality Protection Act (FQPA) of 1996 [3] directs US-EPA to consider the need for an additional safety factor of up to ten-fold (10x) in its tolerance assessments, to account for uncertainty in the data base relative to sensitive groups such as children, unless there are ‘reliable data’ on children’s toxicity and exposure that support the use of a smaller factor or no additional safety factor at all.
In a recent report (2004), titled ‘Pesticides in food; assessing the risk to children’, the Dutch Health Council [4] recommends that the use of an additional safety factor is appropriate if, on the basis of the available toxicological data and in the absence of adequate research, there is reasonable cause for supposing developing organisms to be more vulnerable than adult organisms. The Council recommends that for each individual pesticide, the completeness of the database should be assessed by experts.

This report describes child-specific toxicokinetics, toxicodynamics and exposure, and addresses the adequacy of, and the data gaps in the present methods of risk assessment. This guidance document is intended to make risk assessors aware of the different aspects that should be taken into consideration when performing a risk assessment of a chemical with respect to children. In the document, guidance is provided for risk assessors on the strategy that may be used when a risk assessment for children is performed, thereby stimulating the consistency in evaluations. In addition some issues relevant to the risk management of chemicals are discussed.
In the document a number of recommendations for improvement of risk assessment for children are made.

2. Exposure

It is apparent that the risk a chemical poses to the health of children is dependent not only on its child-specific toxicity, but also on the level of exposure. Whether children should be considered as a specific sub-population in risk assessment of chemicals should therefore in first instance be based on the exposure profile of children and not on the hazard profile of a chemical (only). Since the demand for nutrients and oxygen, the dietary pattern, and the behavioural activity and pattern differ between children and adults, the exposure pattern and exposure levels of children may substantially differ from that of adults [5].

2.1 Caloric, nutrient and oxygen demand

Due to the rapid growth and development of children, exposure between children and adults, but also between children of different age groups may differ considerably. Children consume more food and drink more fluids per kg body weight than adults do. Children from 0-6 months of age have the highest food and water intake and respiratory rate on a mg/kg bw basis. Accordingly, chemical contamination of food, drinks and air will lead to relatively high exposure in this age groups. With increasing age food, water and air intake gradually decline to adult levels.
Due to their small size and rapid growth children have a relatively high oxygen demand and accordingly a high inhalation rate. For chemicals which are airborne, children may be higher exposed via the inhalation route than adults.
The high body surface to body weight ratio in children may result in a higher systemic levels of a chemical following dermal exposure.
These child specific characteristics should be taken into account in the exposure assessment of a chemical.

2.2 Oral exposure and dietary pattern

Apart from the quantitative differences in food intake between children of different ages, and between children and adults, also the qualitative dietary intake varies considerably. Shortly after birth the variation in the diet is very limited, i.e. it consists predominantly of breast milk or powdered milk. Gradually other food products such as fruit, cereals (bread, porridge) et cetera. are included in the diet. This implies that if a certain food source for these very young children contains a certain substance (e.g. dioxins in breast milk), this may lead to high levels of exposure. On the other hand, chemicals in certain other food sources will never reach very young children because they do not consume those food stuffs. From about one year of age the variation in the diet of children is more or less similar to that of adults, although relative quantities still may vary. Recently, a food consumption survey in children aged 8-12 months was performed by RIKILT [6]. In another food consumption survey by TNO in the Netherlands, the food consumption of children of different age groups (8-10 months, 11-13 months, 17-19 months) was assessed [7]. However, these data are not freely available.
In a food consumption survey in the Netherlands, scheduled for 2005, the food consumption of children aged 2-6 years will be included. Data from such food consumption surveys will

certainly improve the exposure assessment for children of a certain age group to a chemical through food consumption.

It is recommended that, where available, data on food consumption of children of different age groups (e.g. 8-12 months) should be included in the risk assessment of a chemical.

2.3 Other routes of exposure and behaviour

Children may be exposed to a chemical through a different route as adults. The route of exposure may affect the potentially toxic effects of a chemical, both in adults and children. For example, the level of systemic exposure to a chemical may differ due to different levels of absorption following oral, dermal and inhalation exposure. Also, the systemic level of a chemical may significantly be affected by the presence of a first pass effect in case of oral exposure, or absence of a first pass effect in case of dermal or inhalation. Therefore the route of exposure of a child should be taken into consideration, in particular when the exposure route may differ from that of adults.
Differences in behaviour between children and adults but also between children of different age groups may lead to considerable differences in exposure. For instance, children of 9-18 months of age display the most crawling behaviour [15], making this age group particularly vulnerable to dermal exposure from contaminated objects and surfaces. Accordingly, treating a room with a substance by using a spray-can may lead primarily to inhalatory exposure in adults during application of the spray. However, due to their behaviour, young children may be predominantly exposed through the dermal (crawling) or oral (mouthing) route when they are present in the room afterwards.
Children may also be more exposed to toxic substances than adults since children spend more time in the same room or area, are in closer contact with a contaminated surface (e.g. by crawling) and display less hygienic behaviour (mouthing of hands, objects, surfaces; pica behaviour). On the other hand, when a chemical is only used in an occupational setting, children may not be exposed at all to the chemical, or only indirectly, for instance through contaminated clothes of their parents. When performing an exposure assessment, consequences of the behaviour of the children of a specific age group on the exposure should be considered. It is recommended that the child specific inhalatory rate and body surface/body weight ratio are taken into account when performing a risk assessment for children for substances to which children are exposed through the inhalatory or dermal route. For more information on exposure scenarios and corresponding default parameters for children, see Prud'homme de Lodder and Van Engelen [8].

2.4 Strategy for exposure assessment

From the above it follows that depending on a number of factors (e.g. the source of the substance, caloric demand, the behaviour, the route of exposure), children of a certain age group may be highly exposed to a chemical. When performing an exposure assessment for children, the following strategy could be used.

- Determine what is/are the source(s) of exposure, and whether the chemical can be transferred to the child. The presence of a chemical in a certain product or matrix does not necessarily mean that the child will be exposed to it. Data on the level and time course of leaching of the chemical from the product or matrix may refine the exposure assessment.

- Based on this information, determine what may be the route(s) of exposure, i.e. oral, dermal, inhalatory or a combination of these. For instance, is the chemical present in food that children regularly eat and drink? Is it present in residential or school air, or in soil and dust in and around residences, schools or play areas? Is it present in products children use? Note that the source of exposure will determine whether children of a certain age group will or will not be exposed. E.g., very young children (<8 months) are not likely to be exposed to chemicals in/on playground structures.
- Determine which age groups will be primarily exposed. Then prepare an exposure scenario for those specific group(s) and estimate the level of exposure. For chemicals present in food, child-specific food intake data from food consumption surveys should be used. For non-food sources of chemicals such as consumer products, reasonable worst-case estimates of exposure levels of children can be obtained by the use of mathematical consumer exposure models, e.g. ConsExpo [9]. By default use the group with the highest exposure in the risk assessment. Nevertheless, it should be stressed that the age group that has the highest exposure levels is not necessarily most at risk since the sensitivity to the adverse effects of the substance also varies between children of different ages. This has to be considered on a case-by-case basis.

2.5 Recommendations with respect to exposure assessment.

In general, the exposure assessment of children as it is currently performed, should be improved, and should be a more routine procedure.
At present, for children of 1-6 years of age, exposure to a chemical through food intake is taken into account. It is recommended that this is also done for children aged 8-12 months, for whom dietary intake data are now available in the Netherlands.
For non-food sources of chemicals such as consumer products, exposure of children should also be taken into account. Reasonable worst-case estimates of exposure levels of children can be obtained by the use of mathematical consumer exposure models, e.g. ConsExpo.
More exposure data for children of different ages, exposed through different routes are needed to refine the child-specific exposure assessment. This includes data on the level and time course of leaching of a chemical from a product. These data can be included in mathematical exposure models such as ConsExpo.

It should be realized that, in particular for young children exposure during a short period of life may be rather high in comparison with adults. When performing a risk assessment for children, this short-term high exposure is often compared with limit values based on chronic toxicity data (e.g. an ADI). In such a case, it should be realized that this may result in a conservative risk assessment.
Furthermore it is necessary that child-specific inhalatory rate and body surface/body weight ratio are taken into account when performing a risk assessment for children for substances to which children are exposed through the inhalatory or dermal route.
In addition to the physiological characteristics that influence the exposure, also the effect of the behaviour of children of a specific age group on the exposure should be taken into account in the exposure assessment. However, this information on behaviour and time-activity patterns is scarce.

3. Toxicokinetics

The physiological differences between children and adults may affect the kinetics of a substance in the body [10]. This may result in a higher or lower internal exposure of children.
For instance, oral absorption of a substance may be affected by the gastric pH, gastric emptying rate, concentration of digestive enzymes and gut flora. The high body water content, the low plasma protein binding capacity and the permeability of the blood brain barrier in children may affect the distribution of a chemical. The immaturity of the metabolic enzymes in the liver and the low renal blood flow and glomerular filtration rate may affect the elimination of a chemical. As compared to adults, the largest differences in the values of the above mentioned parameters are observed in neonates. Most of the values approach adult levels within 6-12 months.
Most toxicological data are obtained from studies in which the substance was administered through the oral route. When the exposure of a child (or adult) is expected to occur via inhalatory or dermal exposure a route-to-route extrapolation may be required. In such a case the route-specific and age-specific toxicokinetics should be taken into account.
For the majority of chemicals information on their kinetics in children of different age groups is lacking. Accordingly, toxicokinetics of a chemical in children generally is not considered in risk assessment. At present, differences in toxicokinetics of a chemical between children and adults are assumed to be accounted for by the intra-species safety factor. Although there is considerable information on the physiological differences between children and adults, and how these differences may affect the kinetics of a chemical, this knowledge is not routinely used in risk assessment of a chemical for children. In this respect, the use of Physiologically Based PharmacoKinetic (PBPK) models could refine the internal exposure assessment and therefore improve risk assessment of a chemical. Because PBPK modelling is not always a easy to use tool, internal exposure assessment for children using PBPK modelling should not be included in the standard risk assessment procedure. However, it can be very valuable method when refinement of the risk assessment is necessary (e.g. in the case that the routine risk assessment shows possible risks for children).

3.1 Strategy for kinetics

In the risk assessment for children, with respect to toxicokinetics the following strategy could be used:

- First of all, establish whether there are data available on absorption, metabolism, distribution and excretion of the chemical in children of a specific age group that are exposed to the chemical. Determine to what extent the toxicokinetic parameters in children differ from those in adults. These data may indicate whether internal exposure of children may be more or less as compared to adults. It has to be noted, however, that for most chemicals (with the exception of pharmaceuticals) no data will be available on toxicokinetics in adults, let alone in children.
- If only toxicokinetic data in adult humans are available (the default condition for most chemicals), determine whether there are indications that kinetics of the chemical may differ substantially between children and adults? For instance, the levels of the enzymes involved in the metabolization of the chemical may be low in babies.

- If no human toxicokinetic data are available, consider whether toxicokinetic data from animal studies indicate if children may be higher exposed to a chemical than adults.
- If available, consider information on toxicokinetics in humans or animals from structurally related compounds (read-across concept).

If there are substantial indications (e.g. from related compounds) that children may encounter a higher internal exposure of the toxic compound compared to adults, the risk assessor should evaluate whether the default extrapolation factor for intraspecies variation is sufficient. This can be done both in setting limit values or in the evaluation of the a margin of safety.

3.2 Recommendations with respect to toxicokinetics in risk assessment

In order to refine the risk assessment of a chemical, the differences in toxicokinetics of a chemical between children and adults could be taken into account. As toxicokinetic data in children are generally not available, estimates of internal exposure to a chemical in children, and differences in internal exposure as compared to adults could be obtained from PBPK-models. In addition, an indication of the differences in toxicokinetics between children and adults can be obtained from toxicokinetics studies using juvenile and adult animals. As yet, such studies are neither available nor required.

4. Toxicodynamics

With respect to toxicodynamics, i.e. the effect that a chemical has on the body (organs, tissues), attention has focussed in the last decade on the influence of chemicals on young children. A chemical may induce adverse effects in children at doses lower than those needed to induce similar effects in adults. Furthermore, a chemical may induce other adverse effects in children that are not induced in adults. In particular, a major concern is the influence that a chemical may exert on the developing organs and systems in young children. Disruption of proliferation, differentiation, migration and maturation of cells may have severe and irreversible consequences. In humans, the development of certain organs or systems, e.g. the respiratory tract, the immune and endocrine systems and the brain, continues long after birth. Data on the effects of a chemical on developing systems are obtained from reproduction toxicity studies and (neuro-)developmental toxicity studies in animals.

4.1 Toxicodynamic data gaps

At present, the toxicological profile of a chemical is predominantly based on animal tests. The extent of the database on toxic effects will differ depending on the type of chemical. For drugs and pesticides in general an extensive toxicological dataset is available. For other substances often the toxicological dataset is more limited.
In the toxicity tests a broad range of parameters is included in order to gain a ‘complete’ overview of the toxic potential of a chemical. One should realize however, that the toxicological profile will never be fully investigated. Recently, attention has focussed on a number of important toxicological parameters that are not included in the present set of animal toxicity tests.

Carcinogenicity

In the standard carcinogenicity test (OECD 451) and combined chronic toxicity/carcinogenicity test (OECD453) treatment with the substance test starts when animals are 6 weeks old. Exposure during early life stages is thus not included. Studies in animals have shown that exposure during a very early life stage to methylene chloride or vinyl chloride increased the tumour incidence as compared to a similar exposure at a later life stage [11, 12]. Recent data from animal studies suggest increased susceptibility to cancer from early-life exposure, in particular to mutagenic chemicals [13]. How to incorporate this knowledge into the present day risk assessment needs further attention. When data on the effects of exposure to a certain chemical on childhood or juvenile animal carcinogenicity are available, this information can be included in the risk assessment. However, for most chemicals this information will not be available.

Immunotoxicity

There are indications that the incidence of diseases of the immune system is increasing. Exposure to chemicals has been named as one of the possible causes for this increase. As yet, only a limited number of immunotoxicological parameters (e.g. spleen weight and histopathology) are determined in the set of standard toxicity tests required for chemicals. More scientific research into the disrupting effect of chemicals on the immune system is needed to get a better insight in the extent and seriousness of the problem. Based on these insights it can be decided which endpoints are most suited to address this issue and how changes in these parameters should be interpreted.

Endocrine disruption

Endocrine disruption refers to health effects that may be mediated by mechanisms affecting hormone homeostasis. Children may be especially vulnerable in this respect as their homeostatic mechanisms are immature. Indeed, animal studies have shown greater sensitivity of young animals to the effects of hormones. For instance, the uterus of young female rodents is more sensitive to the trophic effects of estrogens.
The sensitivity of this model is high because of the presence of functional estrogen receptors in combination with the absence of endogenous estrogen production. The extrapolation of these findings for the situation in children is still a matter of dispute.
Accordingly, the relevance of new test systems using young animals to detect effects of chemicals on endocrine disruption for the risk assessment process has yet to be established.

Risk assessment of chemicals for children would be improved if more endpoints that are relevant for children would be included in the toxicity studies in animals. At present, reproduction and developmental toxicity studies in general are available for a large number of compounds, which may reveal adverse effects of a chemical on the developing organisms. However, in these studies only a limited set of endpoints is considered (namely the reproduction and structural developmental endpoints), which may not be the compound specific endpoints as identified in regular repeated dose toxicity studies. Also carcinogenicity is not assessed in animals that are exposed early in life.
The investigation of a broader set of toxicological parameters in the multi-generation toxicity test, especially of those parameters that are affected in (sub-)chronic toxicity studies may provide at least part of the information on developmental effects of chemicals that is lacking at present. The study protocol for the multigeneration reproduction toxicity studies, could also be modified to include parameters indicative for effects on the developing immune and endocrine systems.
A prerequisite for such alterations to the study protocols is that international agreement is reached on the endpoints to be included in the study protocols. Reliable test systems should be developed, validated and internationally accepted. Current experience with the OECD426 draft guideline for developmental neurotoxicity has shown that this is not a straightforward issue. The addition of new parameters to existing test protocols meets with the problem of the limits of practicality in terms of the amount of assessments that can be done within the time frame of a study on the one hand, and with a statistically necessary minimum of data points on the other. Furthermore, there should be consensus on the thresholds of adversity for each of the endpoints, since in particular the central nervous system, the immune system and the endocrine system may react very easily to external stimuli. Guidance is needed to distinguish between a physiological response and an adverse effect.

In view of the developmental landmarks occuring uniquely during the development of a child, it seems reasonable to assume that neonates may have a specific vulnerability to the development-disrupting effects of chemicals dependent on their age. However, at present little information on the sensitive windows for the effects of chemicals on the development of organs is available. In view of the prolonged periods of development that have been reported for some organs and systems in children (e.g. brain, lungs, immune system), it is difficult to establish which age group is most vulnerable in this respect. Moreover, it has to be noted that the age group that is most sensitive to the toxicodynamic effects of a substance is not necessarily most at risk since exposure levels may differ substantially between children of different age groups.
It should also be noted that critical windows in the development of laboratory animals and children are not necessarily the same. For example, the period of rapid growth of the brain, known as the brain growth spurt, occurs post-natally in rats and mice but starts already from

the sixth month of pregnancy in humans. This knowledge may be of importance for the interpretation of neurotoxic effects observed in young animals. Further research is needed to establish whether the treatment periods used in the present animal toxicity tests adequately cover the sensitive windows in humans.
It should be stressed however, that although children may be more vulnerable to the specific developmental effects of chemicals, such developmental effects may not necessarily be the most criticial effect of the substance. Possibly other effects (for which children and adult do not differ) may occur at lower levels.

Most toxicological data are obtained from studies in which the substance was administered through the oral route. However, the severity and nature of an adverse effect of a chemical may dependent on the route of administration. For instance, if a chemical induces local effects in the lung, toxicity data obtained after oral administration may not be applicable. Under these circumstances the toxicodynamic effects of a chemical caused by exposure through one route of administration can not be predicted on the base of route-to-route extrapolation from toxicodynamic data obtained through another route of administration. In such a case a toxicity study in which the chemical is administered through the relevant route is required. Since children may be exposed through a different route than adults, this route should also be taken into account in the risk assessment.

4.2 Strategy

In risk assessment of a chemical, with respect to toxicodynamics the following strategy could be used:

- Evaluate the total database. Also consider toxicity data from structurally related chemicals.
- Consider whether available toxicity studies are relevant with regard to the expected route of exposure.
- Determine whether there are indications that the chemical may induce adverse effects in children. Define these effects. Also consider whether the mode of action for the adverse effects of the chemical in adults (human or animal) is a cause for concern for children. For instance, if a chemical is known to affect the immune system in adults, it may have more consequences for the developing immune system in children.
- Determine whether the database on the effects on children is complete, with respect to the data requirements. If not, define which additional studies, measuring which specific endpoints, are required. If it is possible within the legal framework, request additional data.
- Determine how the NOAEL for potential adverse effects relevant for children compares to the overall NOAEL for all other adverse effects induced by the chemical. In view of this comparison, determine whether the potential effects in children are a cause for concern.

Based on the considerations above, an additional assessment factor may be applied if there is a substantiated concern that the standard assessment factors do not sufficiently cover the differences in toxicodynamics between children and adults.

4.3 Recommendations with respect to toxicodynamics in risk assessment

In order to improve the risk assessment of a chemical, a number of improvements in the toxicodynamic data base can be made.
The most direct way is to investigate a broader set of toxicological parameters in the multi-generation toxicity test, especially of those parameters that are affected in (sub-)chronic toxicity studies may provide at least part of the information that is lacking at present.
Research is needed into which additional toxicological parameters (e.g. immunological or endocrine) may be included in the multigeneration reproduction toxicity studies, from the perspective of risk assessment of chemicals for children. A prerequisite for the inclusion of such additional parameters is that, firstly, the additions to the present multigeneration reproduction study protocol are internationally accepted and secondly, there is international consensus on the interpretation of effects on the endpoints.
Also other studies in juvenile animals could be used to obtain information on possible effects of a chemical in children. This field is receiving increasing interest and should be further exploited to determine practical routes and techniques of exposure which are both relevant for extrapolation to man and which are not disturbed by secondary handling-induced stress to juvenile animals. It is recommended that further guidance on the use of specific juvenile animal studies in risk characterization and risk assessment is developed. It is noted that the desire for additional data from animal studies contravenes with the current movement to decrease the use of animals in toxicology.
In addition, research is needed to establish whether the treatment periods used in the animal toxicity tests adequately cover the sensitive windows in humans. For this it is necessary to establish what are the sensitive windows for critical endpoints in children as well as in young animals.

5. Risk assessment for children

In the risk assessment process the exposure and toxicity data are integrated to establish whether a chemical may pose a health risk to humans. The specifics with respect to toxicokinetics, toxicodynamics and exposure have been dealt with in chapters 2-4. In the risk assessment process for chemicals present in food acceptable daily intake levels (ADI or TDI, for chronic daily exposure) and acute reference doses (ARfDs, amount of a chemical that can be ingested within 24h without appreciable health effects) are established. For chemicals present in non-food sources the margin of exposure (MOE = overall NOAEL/exposure level) of a chemical is estimated and it is determined whether the MOE is a cause for concern for the health of the human population.
It is clear that the sensitivity to the adverse effects of chemicals may differ between different groups in the population. In chapters 2, 3 and 4 it is indicated that children are potentially more or less sensitive to the effects of a chemical. It should be kept in mind that at present in risk assessment of chemicals the existence of potentially susceptible groups in the human population, such as children, is already taken into account. The exposure level that is considered safe for humans is usually based on the overall NOAEL from animal studies, divided by an assessment factor of 10 for interspecies differences (extrapolation form animal to average human) and a factor of 10 for intraspecies differences (extrapolation from average human to sensitive human). However, for each chemical, in the risk assessment process it should always be considered whether children are sufficiently protected by the default inter- and intraspecies factors, or whether the application of an additional assessment factor is warranted. The use of additional factors is already a possible approach in the current risk assessment practice. The use of an additional safety factor should however always be justified.
The strategy that can be used in hazard and exposure assessment of chemicals with respect to toxicokinetics, toxicodynamics and exposure has been discussed in chapters 2, 3 and 4, respectively. In Figure 1 a decision tree is depicted which can be used to determine whether an additional safety factor is needed to protect children for the adverse affects of a chemical.

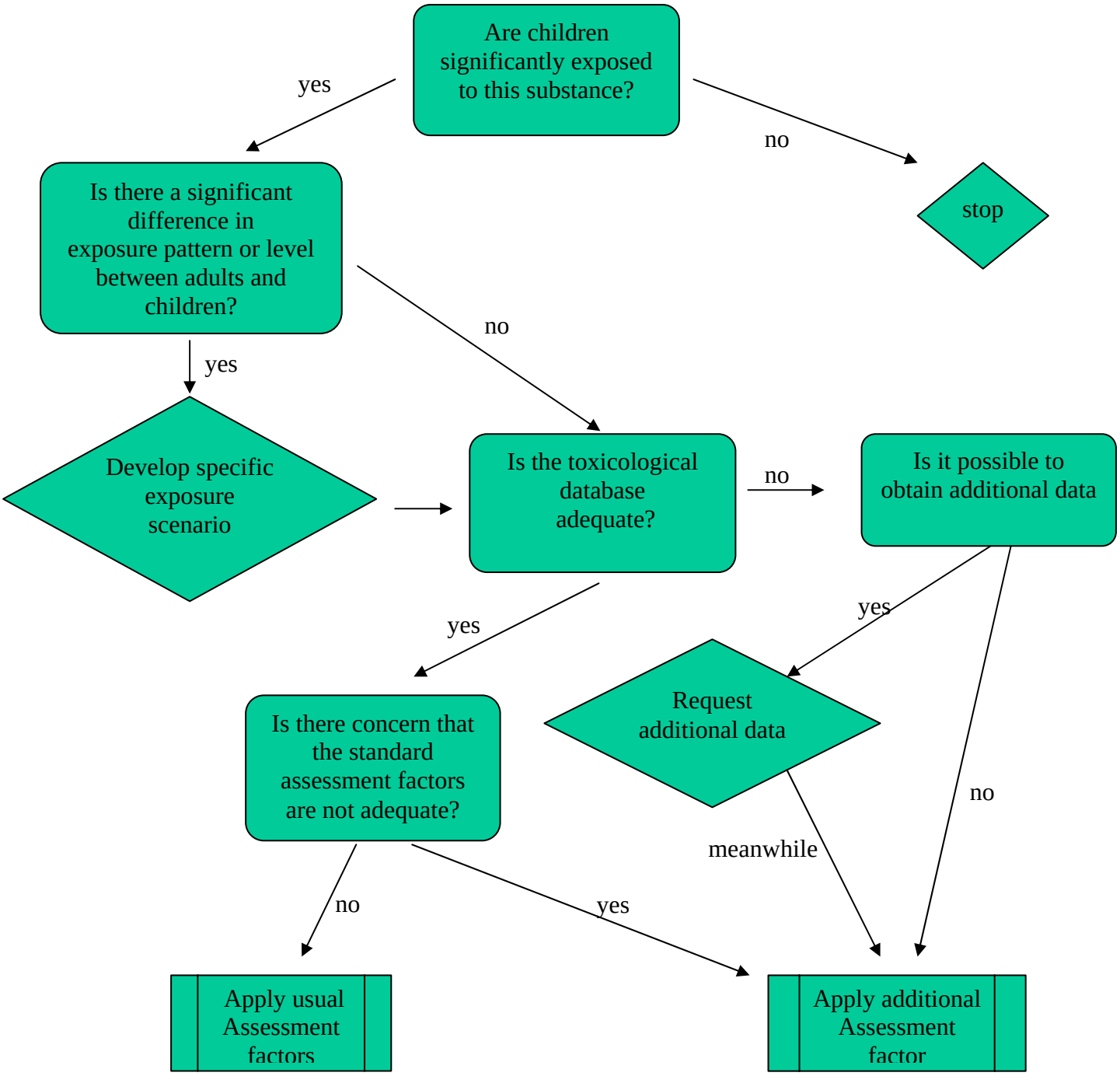

Figure 1. Flow diagram for risk assessment of chemicals in children

In the present chapter a number of aspects that are relevant in the process of risk assessment or risk management are discussed.

5.1 When do we need to perform an additional risk assessment for children?

Risk assessment of a chemical comprises exposure to as well as toxicity of the chemical. Children may be exposed at higher levels or through different routes than adults, or they may be more susceptible to the compound in question. In both instances, a specific risk assessment for children is needed.

5.2 What is the purpose of the risk assessment?

When performing a hazard or risk assessment for a chemical it is important to start by defining the scope of the assessment. Is the assessment performed for authorization purposes (including establishing an ADI, Acceptable Operator Exposure Level (AOEL) or Maximum Residue Limit (MRL)) or is an actual risk assessment performed, e.g. exceeding the established limit values for a chemical. In the first example, worst case estimates may be sufficient, whereas in the second example realistic estimates should be used.
Furthermore, it should be made clear whether the assessment refers to all possible sources and routes of exposure (i.e. aggregate exposure) or only to a specific exposure scenario.

5.3 Which age groups should be taken into account?

The age groups that should be taken into consideration, depends on the nature of the exposure and the toxicological endpoints of the chemical.
Since children at certain ages have different diets and show behaviour (e.g. crawling, sucking, etc), which is different to that of adults they will be differently exposed, and therefore the exposure characterization needs special attention [8]. It should be assessed which type of exposure scenario is relevant for the product and/or chemical under study. From this exposure scenario, the relevant age group will be identified. For example, crawling behaviour is relevant with respect to risk assessment of flea spray that is applied to carpets. In this case, children in the crawling age might be more at risk than adults, since in contrast to adults, these children are (higher) dermally exposed to the product. For risk assessment of residues of wood preservatives on playing grounds, it is evident that another group of children should be focussed on, namely the group of children that spend most time playing outdoors.
On a similar note, it is important to take into consideration on which toxicological endpoint the acceptable exposure levels are based. If the acceptable exposure level is based on developmental effects, the age group that may be most at risk are likely to be neonates, and exposure of, for instance, toddlers may be of less concern. However, it should be kept in mind that the critical windows of development may differ between animals and humans (see below).

5.4 The use of human data

If available, human data on the toxicity of a chemical are very valuable, in particular when these data provide information on endpoints, such as slight airway irritation, language skills, psychopathology and intelligence, that can not be measured (easily) in laboratory animals. Data may be obtained for instance from toxicity studies in volunteers, health monitoring programs on workers of manufacturing plants or epidemiological studies. It must be noted however, that except for pharmaceuticals, in general very few data are available from studies in adults, let alone children. Epidemiological studies may provide information on the adverse effects of a chemical on the human population. However, it is often very difficult to ascribe, beyond doubt, adverse effects in humans to exposure to a certain chemical. Every day, humans are exposed to many (unknown) chemicals in varying concentrations. In order to link an adverse effect in the human population to exposure to a particular chemical, the exposure must be well described, with respect to route, level, exposure duration and frequency, and the effect must be quite substantial before it can be detected.

5.5 The use of juvenile animal studies

In the absence of human data, information on the potentially increased sensitivity of children to a chemical may be obtained from studies in juvenile animals. In a number of toxicity tests, which are described in OECD guidelines 415, 416, 421, 422 and 426 (draft), juvenile animals are exposed to the test article. However, for a number of reasons, these standard animal tests can not always predict all adverse effects of the chemical. For instance, the standard animal tests do not always include all relevant parameters, such as immunotoxicity or lung development. When there are indications that a chemical may interfere with the development of certain organs or systems, for instance on the basis of human data or regular animals studies, or on the basis of structural similarities with other chemicals, then performance of specific, tailor-made juvenile animal studies may be called for. Such a study may provide information on the relative susceptibility of a young animal compared to adults, and possibly on the (ir-) reversibility of the effect. Such studies need not to be included in the set of standard toxicity tests, but should performed only when data should indicate the need for such a test (see also [14].

It is noted that the demand for additional data from animal studies contravenes with the current movement to reduce the use of animals in toxicological research. On a broad level, non-governmental organisations support the increased use of alternative methods to test various kinds of chemicals and to reduce the total number of animals. However, it can be questioned whether less animal data and/or the use of alternative test methods provide sufficient information for an adequate risk assessment of children as argued above.
At present, national and international legislation determines the data requirements for different classes of chemicals. If it should be deemed necessary to extend the toxicological data requirements in order to improve the risk assessment for children, as a consequence legislation may have to be adapted accordingly.
It is recommended that further guidance on the use of specific juvenile animal studies in risk characterisation and risk assessment is developed.

5.6 Exceeding health based limit values, and risk management options

If the exposure of children of a certain age group exceeds a limit value/ acceptable exposure level (e.g. ADI, ARfD), it may be necessary to take regulatory actions. However, in such a case there are a number of points the regulator could consider.

First of all, it is worth while to consider the critical endpoint on which the acceptable exposure level is based. For instance, in case an ARfD is based on embryo/fetotoxicity in a developmental toxicity study, such an ARfD would apply specifically to women of childbearing age. Exceeding this ARfD may not pose a health risk to children of 1-6 years of age. In such a case it may be necessary to consider the toxicological data base of the chemical to establish whether there are other toxic effects that would be of relevance for children of the concerned age group. For this endpoint it has to be established what the limit value would be, and compare this with the exposure of the children of the age groups of concern in order to decide whether regulatory measures are required.

The nature of the endpoint on which the limit value is based may indicate the urgency to take regulatory steps. In case a limit value is based on a critical effect that is likely to be the result of long term exposure, e.g. a reduced body weight gain, an occasional exposure above the limit value is not likely to pose a serious health risk. On the other hand, if the limit value is based on acute effects in animal or human studies, exposure exceeding the limit value can not be dismissed, and regulatory measures may be required. Another point to be taken into consideration is the seriousness of the adverse effect. When exposure to a chemical is likely to induce irreversible damage, the urgency to take regulatory steps may be much higher than when the adverse effects are transient and reversible.

Another piece of information that may be taken into account in the risk management is the extent of the problem. Will the exceeding of the limit value affect a large part of the human population or is a small subgroup at risk? This information may affect the type of regulatory steps that are taken. Such an estimate of the subpopulation at risk may be provided through probabilistic exposure or risk assessments.

6. Conclusions and policy implications

The present guidance document describes, in general terms, the various aspects that are important for risk assessment of a chemical with respect to children. It aims to make risk assessors aware of the different aspects that should be taken into account when performing such a risk assessment. However, the exposure, hazard and risk assessment of a chemical is a complex process. Each individual chemical may have its specific characteristics and problems, and it is not possible to determine a general procedure how to deal with each individual chemical. Therefore it necessary that the risk assessment of a chemical remains to be performed by experts.
In this report it is stated that – based on scientific grounds - a separate risk assessment for children should be performed for all chemicals that provide a significant difference in exposure pattern or level between adults and children. It is apparent that the risk that a chemical poses to the health of children is dependent on the level of exposure, the toxicokinetics and the sensitivity of the specific age groups to the chemical. Accordingly, it is necessary to be able to determine the level of exposure in children of different age groups and to have insight in the sensitivity of these age groups to the toxic effects of the chemical. There are exposure models that also estimate exposure levels in children (e.g. ConsExpo), however more data on child-specific exposure parameters would improve these exposure estimates.
Some toxicological effects of chemicals may be missed using the current testing protocols. Although development-disrupting effects of a chemical may be revealed by reproduction-teratogenicity- or developmental neurotoxicity tests in animals, it should be noted that these test only address a number of specific parameters to be measured.

All together, the present report indicates that risk assessment of chemicals for children leaves room for improvement. This, however, does have a number of implications.

1. In order to refine the risk assessment of chemicals for children, more data are needed, for instance on the exposure of children, on the dietary intake (i.e. quantity and quality) of children of different age groups, on the influence of early exposure of chemicals on carcinogenic risk, on the developing immune system and on hormone systems et cetera. Such data are currently not available or not systematically put together. This requires funding of research into these matters, and international agreement on how to incorporate this knowledge into risk assessment.
2. Additional data can be collected by a smart combination/adaptation of tests (e.g. extending the current protocols, or combining the 90 day study with a developmental study). Extending the number of parameters measured in a toxicity test will increase the costs of the test. However, as compared to performing separate tests the costs will still be lower, financially as well as in number of animals required.
3. Filling in the data gaps may require adaptation of the present (OECD) guidelines for toxicity tests (e.g. inclusion of additional parameters in the reproductive toxicity tests) or the demand for additional toxicity studies (e.g. on immunotoxicity and endocrine disruption, juvenile animal toxicity studies).
4. If additional data are needed in order to improve the risk assessment for children, it is necessary to extend the toxicological data requirements in several frameworks. As a consequence legislation may have to be adapted accordingly. It should be realized that this may be a time-consuming process requiring international harmonisation.

5. Extending the toxicological data requirements, however, is at odds with the current trend to reduce the use of animals in toxicity testing. Especially since there is an increasing tendency to skip in vivo testing of chemicals and to use in vitro testing or other alternative methods. However, it may be questioned whether toxicological endpoints such as immunotoxicity or neurodevelopmental toxicity could be addressed adequately without testing in vivo.
6. Routinely incorporating a risk assessment of chemicals for children in the risk assessment procedures will increase the time needed to perform a risk assessment.
7. Performing a specific risk assessment of chemicals for children will increase confidence of the consumer and regulatory bodies that products are safe.

It is recommended that the different regulatory bodies strive after a harmonized approach to the risk assessment of chemicals for children. This should be done on an international level, e.g. the International Programme of Chemical Safety (IPCS), and should not be limited to specific frameworks.

7. National and international perspectives

In the present chapter a brief overview is presented on a number of national (RIVM, Dutch Health Council) and international approaches (EU, USA, WHO) on the position of children in risk assessment of chemicals. Also some activities which address the issue of children in the risk assessment of chemicals are described.

The Netherlands

RIVM
In a recent RIVM report [2], 'Risk assessment of chemicals: What about children?', the differences between children and adults with respect to exposure, toxicokinetics and toxicodynamics of chemicals were described. With regard to risk assessment of chemicals it was concluded that, in general, if a full set of toxicological data is available, the presently used assessment factors (10 x 10) are considered adequate in safeguarding the human population. However, the use of an additional assessment factor, e.g. to provide for an incomplete data base, in order to protect the sensitive groups in the human population, among others children, should be considered on a case-by-case basis.
Furthermore RIVM has developed the mathematical consumer exposure model ConsExpo, which allows estimating children's exposure to chemicals from a variety of non-food sources [9]. The model is regularly updated. Also, RIVM has been involved in research on the behavioural activities of young children, which enables a more refined exposure assessment [15].

Dutch Health Council
In 2004 the Dutch Health Council published the report: 'Pesticides in food: assessing the risk to children' [4], which describes the differences in exposure and response to pesticides between children and adults, and discusses the present day risk assessment procedure and its adequacy. The Health Council indicated that the use of an additional safety factor is appropriate if on the basis of the available toxicological data and in the absence of adequate research there is reasonable cause for supposing that developing organisms are more vulnerable than adult organisms. The Health Council indicated that for each individual pesticide the possible harm to development should be assessed by experts.
One of the recommendations of the Health Council was that the current reproduction toxicology test protocol should be adapted to allow for identification of effects on the immune system, the nervous system and the endocrine-regulated processes of development. In addition, it was recommended that food consumption data for children between 6-12 months should be collected and, where necessary, be included in the risk assessment. In this respect it can be noted that recently a food consumption survey for children aged 8-12 months has been performed [6].

European Union

Scientific Committee on Food (SCF), Food Additives
The toxicological data required for food additives and used as the basis for establishing the ADIs covers adequately exposure during all life stages including special emphasis on reproductive cells, on the foetus and on the young and old organism (Comm. of EU, 1980). However, the specific exposure situation with direct exposure of infants to food additives due

to the use in infant formulae intended for use as the sole nutrition for infants below the age of 16 weeks is not included in the standard toxicity test protocols. Therefore a special evaluation beyond the present ADI evaluation is needed before food additives are to be accepted for use in infant formulae for infants in the age 0-16 weeks [16].

Scientific Committee on Food (SCF), Pesticides
The ADI covers all groups of the population. The Committee does not recommend the use of special uncertainty factors for infants and children or the establishment of special ADIs for this age group. The toxicological database should adequately cover the most sensitive effects and the most sensitive age groups and the ADI should cover all sensitive segments of the population, irrespective of age. If there is scientific evidence that infants and children are the most sensitive populations to a particular pesticide, that evidence must drive the derivation of the ADI.
The Committee recognised that the currently used data package for the establishment of the ADI was not in all respects optimal to reflect a particular sensitivity of infants towards the potential toxicity of a given pesticide. However, it was the opinion that in most cases the toxicological studies would have provided indications if such special sensitivities were to exist. The Committee concluded that the current ADIs would provide a reasonable basis for evaluating the health impact of pesticides in foods intended for infants and young children. The fact that infants and children have a relatively higher intake of some food items than adults should clearly be considered in the risk assessment. This is not always taken into consideration when setting MRLs [17].

Remark: it is noted by the present authors that the approach used by the SCF-Food additives differs from the approach used by the SCF-Pesticides.

SCALE (Science, Children, Awareness, EU Legislation and Continuous Evalution)
SCALE is a strategy that was launched by the European Commission with the overall aim to reduce diseases caused by environmental factors in Europe. In order to achieve this goal it is necessary to better understand and identify health problems related to the environmental degradation, which will allow prevention of new health threats linked to environmental pollution. Special emphasis is given to the most vulnerable groups in society, in particular children. The Commission presented a European Environment and Health Action plan 2004-2010 (9 June 2004) [18, 19, 20], comprising 13 action points aimed at improving the co-ordination between the health, environment, and research sectors. The actions are divided into the three following areas:

- **Monitoring:** Developing indicators to measure the link between environment and health and understand the routes pollutants take from their source to the human body. This would for example include ‘biomonitoring’ (taking regular samples of blood, urine or hair) to measure human exposure to environmental pollutants.

- **Research**: Focusing research on four priority diseases (asthma/allergy, neuro developmental disorders, cancers and endocrine disrupting effects) to ‘fill the knowledge gap’.

- **Communication**: Developing citizen’s awareness to help them to make informed health choices. Other actions include training to health professionals to make sure they are alert about environment and health interactions.

PINCHE
The PINCHE-project [21] is a **P**olicy **I**nterpretation **N**etwork on **C**hildren's **H**ealth and **E**nvironment, that is funded by the European Union for three years. The PINCHE project is designed to provide decision makers, environmental health professionals, and other stakeholders with information relevant for policy development. This will help making decisions about issues in the area of children's health and environment.

Environmental pollution potentially has large consequences for children's health, and costs of doing something about it can be very high. Therefore a Network on Children's Health and Environment can play an important role in providing policy makers and other interested parties in society with timely and balanced information about the relationship between pollution and health.
The Policy Interpretation Network will be based on existing research and will contribute to discussion, analyses, and (policy relevant) interpretation of the findings of current research. A network bringing together scientists and representatives of industry, NGOs, patient organisations, policy makers et cetera will be formed.
More information on PINCHE can be found at http://www.pinche.hvdgm.nl/.

USA

FQPA

The US Food Quality Protection Act (FQPA) of 1996 is aimed to protect sensitive groups in the human population, among others children, for the adverse effects of chemicals. The FQPA directs US-EPA to use an additional, tenfold (10X) safety factor in its tolerance risk assessments, unless there are 'reliable data' on (children's) toxicity and exposure that support the use of some other safety factor. Recently, the Office of Pesticides Programs of the US-EPA provided a guidance on the determination of the appropriate FQPA safety factors in risk assessment [22].

CEHI
The Children's Environmental Health Institute (CEHI) [23] has been established to identify, validate, and develop solutions to address adverse health effects to children occurring as a consequence of exposure to hazardous environmental substances.
The CEHI provides an overview of recent reports and studies on children's environmental health on website: http://www.cehi.org/reports.html

VCCEP
The Voluntary Children's Chemical Evaluation Program aims to enable the public to better understand the potential health risk to children associated with certain chemical exposures. The key question of the program is whether the potential hazards, exposures, and risks to children have been adequately characterized, and, if not, what additional data are necessary. Companies that volunteer in this project collect or develop health effects and exposure information on their chemicals and integrate that information in a risk assessment and a data needs assessment. If data needs for exposure or toxicity are identified the companies may choose to volunteer any additional data generation or testing and/or to provide additional assessments. Each submission undergoes review and discussion by a peer consultation panel consisting of a wide range of stakeholders. Meeting reports, summarizing the presentations of

the company, the panel discussions, and any comments from the public, are made available to the public on *TERA*'s Peer review and Consultation website [24].

US-EPA TEACH
The US-EPA has set up the website "Toxicity and Exposure Assessment for Children's Health (TEACH)" [25], which contains information on scientific literature related to 18 chemicals or chemical groups which may potentially affect children's health. The database currently contains about 1500 summaries of scientific publications. Furthermore, the TEACH website provides links to other websites with relevant information. Weblink: http://www.rivm.nl/bibliotheek/rapporten/320005001.pdf

US-EPA Framework for assessing health risk of environmental exposures to children
The US-EPA has released a report which examines the impact of potential exposures during developmental life stages and subsequent life stages [26]. The framework is based upon existing approaches adopted in the 'Framework on cumulative risk assessment' and identifies existing guidance guidelines and policy papers that relate to children's health risk assessment. It emphasizes the importance of an iterative approach between hazard, dose-response and exposure analyses. It improves the scientific explanation of children's risk.

Guidelines for carcinogen risk assessment
The US-EPA has developed new guidelines for carcinogen risk assessment [27], which explicitly call for consideration of possible sensitive subpopulations and/or life stages (such as childhood). For childhood risk a supplemental guidance for assessing susceptibility from early-life exposure to carcinogens has been developed [28]. These guidelines are to be used for all carcinogenic risk assessments that are newly initiated, on a case-by-case base for assessments that currently are being performed or when an updated carcinogenicity risk assessment is being performed [29].

WHO/IPCS

JMPR: The Joint FAO/WHO Meeting on Pesticides Residues requires that for the selection of safety factors for setting an ADI, the Principles for the toxicological assessment of pesticides residues in food [30] (WHO Environmental Health Criteria, No. 104) and JMPR reports should be consulted. According to EHC 104, a 100-fold safety factor (10-fold for interspecies and 10-fold for intra-species) is used as the starting point to extrapolate animal data to man. The intraspecies factor is considered to provide for sensitive human population subgroups. This safety factor may be modified in the light of data that are available. For example, if human data are available the 10-fold factor for interspecies extrapolation may not be necessary. In case the data base is incomplete or of poor quality a higher safety factor may be warranted.

JECFA: The Joint FAO/WHO Expert Committee on Food Additives requires that for the selection of safety factors for setting an ADI, the Principles for the safety assessment of food additives and contaminants in food [31] and JECFA reports should be consulted. According to EHC 70, traditionally a 100-fold safety factor (10 x 10) is used in setting ADIs. The

difference of sensitivity within the human population is assumed to be in a 10 fold range. Again, the 100 fold safety factor may be modified in the light of the available data.

In a recent monograph, ‘principles for evaluating health risks in children associated with exposure to chemicals’(EHC 237, in press[32]), the scientific principles to be considered in assessing health risks in children from exposures to environmental chemicals during distinct developmental stages are evaluated. Furthermore, information for public health officials, research and regulatory agencies, and other experts responsible for protecting children’s health is provided.

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