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Risk Assessment of Chemicals: What About Children?

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Abstract

With regard to risk assessment of chemicals, children are not little adults. Their pattern of exposure (quantitatively and qualitatively), as well as both the toxicokinetics and the toxicodynamics of a chemical will be different, and therefore it should be carefully examined whether children are adequately protected against adverse effects of chemicals.
In this report a concise overview of the relevant data on the differences between adults and children with respect to exposure, kinetics and dynamics of chemicals is presented, and the adequacy of currently used toxicological tests for regulatory purposes is discussed. In addition, in view of the potentially increased vulnerability of children a number of recommendations for further development of risk assessment of chemicals is presented.

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Samenvatting

In de *'regulatory toxicology' (beleidsondersteunende toxicologie)* groeit het besef dat kinderen en volwassenen kunnen verschillen in hun gevoeligheid voor xenobiotica. In het huidige rapport wordt een beknopt overzicht gegeven van de relevante gegevens over de verschillen tussen volwassenen en kinderen met betrekking tot blootstelling, kinetiek en dynamiek van chemische stoffen, en de geschiktheid van de momenteel gebruikte toxicologische testen in het kader van de toelatingsbeoordeling wordt bediscussieerd. Gezien de potentieel andere gevoeligheid van kinderen wordt tevens een aantal aanbevelingen gedaan voor de verdere ontwikkeling van risicobeoordeling.
Binnen het veld van de toxicologische risicobeoordeling zijn er drie belangrijke gebieden waarin kinderen en volwassenen verschillen; blootstelling aan en toxicokinetiek en toxicodynamiek van xenobiotica.
Of in de risicobeoordeling specifiek rekening gehouden moet worden met kinderen is in de eerste plaats afhankelijk van het blootstellingspatroon. Met name de situatie waarin kinderen hoger blootgesteld worden dan volwassenen verdient de volle aandacht.
Kinderen eten en drinken meer per kilogram lichaamsgewicht dan volwassenen, en hun voedingspatroon is anders en minder gevarieerd. Bovendien hebben kinderen een relatief hoge respiratoire activiteit (waardoor er een verhoogde blootstelling via de ademhalingswegen kan optreden) en een hoge lichaamsoppervlak-lichaamsgewicht ratio (mogelijk resulterend in een verhoogde dermale blootstelling). Tevens kan de blootstelling van kinderen aan toxische stoffen hoger zijn dan volwassenen omdat kinderen vaak langer in één bepaalde ruimte of omgeving verblijven, ze zich dichter bij een besmet oppervlak kunnen bevinden (bijvoorbeeld tijdens kruipen over een behandeld oppervlak), en minder hygiënische gedrag vertonen (sabbelen op handen, objecten en oppervlakken; picagedrag).
De route van blootstelling kan bepalend zijn voor het potentieel toxische effect van een stof. In de meeste toxicologische studies ten behoeve van de veiligheidsbeoordeling van een stof wordt de stof oraal toegediend. Echter, bij de opzet van een toxicologische studie moet de route waarlangs het kind naar verwachting wordt blootgesteld in aanmerking worden genomen, aangezien de interne blootstelling aan een stof kan variëren als gevolg van een andere mate van absorptie en de afwezigheid van een 'first-pass effect' na inhalatoire en dermale blootstelling. Een verder punt van aandacht, voor de hele bevolking, maar daardoor ook specifiek voor kinderen, is de totale blootstelling aan een specifieke stof uit verschillende bronnen (geaggregeerde blootstelling), en de blootstelling aan verschillende stoffen met hetzelfde werkingsmechanisme (bijvoorbeeld organofosfaten en carbamaten), de cumulatieve blootstelling.
Door de fysiologische verschillen tussen kinderen en volwassenen kan de kinetiek van een stof in het lichaam beïnvloed worden, waardoor het kind meer of minder gevoelig is voor de toxische effecten van de stof. Bijvoorbeeld, de orale absorptie van een stof kan worden beïnvloed door de verschillen in zuurgraad van de maag, de snelheid van maaglediging, de concentratie van de spijsverteringsenzymen en de darmflora. Als gevolg van de hoge ademhaling en de hoge lichaamsoppervlak-lichaamsgewicht ratio kan de relatieve inhalatoire en dermale blootstelling aan stoffen in kinderen verhoogd zijn vergeleken met volwassenen.
Het hoge gehalte aan water in het lichaam, de lage bindingscapaciteit van het plasmaeiwit en de permeabiliteit van de bloed-hersen barrière kunnen de distributie van een stof in het lichaam beïnvloeden. Het nog niet volledig ontwikkelde systeem van metabole enzymen in de lever, en de lage snelheid van de renale doorbloeding en glomerulaire filtratie kunnen de eliminatie van een stof uit het lichaam beïnvloeden.
Met betrekking tot de toxicodynamiek, dit betreft de effecten van een chemische stof op het lichaam (organen, weefsels), is de invloed die een stof kan uitoefenen op de zich

ontwikkelende organen en systemen in jonge kinderen een belangrijk aandachtspunt. Verstoring van de proliferatie, differentiatie, migratie en maturatie van lichaamscellen kan ernstige en onomkeerbare gevolgen hebben. In de mens vindt de ontwikkeling van bepaalde organen en systemen, zoals de longen en luchtwegen, het immuunsysteem, de endocriene systemen en de hersenen, tot lang na de geboorte plaats. De huidige reproductietoxiciteitstesten en de recent geïntroduceerde ontwikkelingsneurotoxiciteitstest richten zich voornamelijk op de reproductie- en neurotoxische effecten van een stof, en zijn niet ontworpen om bijvoorbeeld immunotoxische effecten, effecten op longontwikkeling en afwijkingen in weefsels en bloed aan te tonen. Wanneer in een toxicologische test de jonge dieren worden blootgesteld aan de stof via de moedermelk, is het opportuun dat wordt vastgesteld dat er relevante hoeveelheden van de stof worden uitgescheiden in de melk. De kritische periodes in de ontwikkeling van proefdieren en kinderen komen niet noodzakelijkerwijs overeen. Hiermee moet rekening gehouden worden bij het bepalen van de blootstellingsperiode van het proefdier in een toxicologische studie.
Aangezien er bij zoveel processen verschillen kunnen optreden tussen kinderen en volwassenen, en het niet duidelijk is wat het uiteindelijke resultaat is, is er niet voldoende informatie om een kwantitatieve ‘overall’ uitspraak te doen met betrekking tot verschillen in gevoeligheid. Bijvoorbeeld, ook al wordt een stof beter opgenomen in een kind, dan hoeft er nog geen sprake te zijn van een verhoogd risico, indien er nauwelijks vorming van een toxische metaboliet plaatsvindt of de uitscheiding van de stof ook verhoogd is.
Men moet zich echter wel realiseren dat bij de huidige risciobeoordeling de default assessment factor 10 voor intraspecies verschillen betekent dat het ‘meest gevoelige kind’ verondersteld wordt 10x gevoeliger te zijn dan een ‘gemiddeld persoon’ uit bevolking, en er derhalve rekening gehouden wordt met een 100-voudige variatie in gevoeligheid in de hele bevolking. Bovendien wordt bij de extrapolatie van de dierexperimentele gegevens naar de mens ook een factor 10 gebruikt, waarbij verondersteld wordt dat de ‘gemiddelde mens’ een factor 10 gevoeliger is dan het ‘meest gevoelige proefdier’ dat getest is. Wanneer een volledige toxicologische dataset beschikbaar is, wordt in het algemeen verondersteld dat de gebruikte assessment factoren (10 x 10) voldoende zijn om de bevolking te beschermen. Echter, het gebruik van een additionele assessment factor om de gevoelige groepen in de samenleving, waaronder kinderen, te beschermen moet altijd in overweging worden genomen, op een ‘case-by-case’ basis.
Voor de toekomstige ontwikkelingen in risicobeoordeling van stoffen wordt, met betrekking tot kinderen een aantal aanbevelingen gedaan. Voor zowel volwassenen als voor kinderen is meer inzicht in de specifieke blootstellingsscenario’s noodzakelijk. Daarnaast dient een beslisboom te worden opgesteld die gebruikt kan worden bij de beoordeling van stoffen om te toetsen of het toxicologische pakket en de kennis over de specifieke blootstelling voldoende zijn om een adequate risicobeoordeling voor kinderen op te stellen.
De geschiktheid van de toxiciteitstesten in jonge proefdieren moet worden onderzocht. Een vergelijking van de dosis-respons gegevens en de NOAELs van testen in volwassen en jonge dieren kan inzicht geven in de spreiding van de intraspecies variatie met betrekking tot leeftijd. Aangezien er voor farmaca veel humane data beschikbaar zijn, is het zinvol om de ontwikkelingen te volgen in het veld van de kinetiek en de dynamiek van farmaca ten behoeve van kinderen. Door gebruik te maken van de distributie van fysiologische en kinetische parameters en van farmacologisch-farmacokinetische modellen (PBPK modellen) die gebaseerd zijn op de fysiologie van kinderen kan worden vastgesteld welke subgroep van kinderen het hoogste risico loopt bij blootstelling aan een bepaalde chemische stof.

Summary

In regulatory toxicology there is increased awareness and concern that children and adults may differ in their susceptibility to xenobiotics. In this report a concise overview of the relevant data on the differences between adults and children with respect to the kinetics, dynamics and exposure to chemicals is presented and adequacy of currently used toxicological tests for regulatory purposes is discussed. In view of the potentially increased vulnerability of children a number of recommendations for further development of risk assessment of chemicals are made.

There are three major areas in which children and adults differ: exposure to and toxicokinetics and toxicodynamics of xenobiotics. Especially the situation in which children are higher exposed than adults this needs full attention.

Children consume more food and drink more fluids per kg body weight than adults, and their dietary pattern is different and less varied. Moreover, children have a relatively high inhalatory rate (which may lead to a higher inhalatory exposure) and a high body surface-body weight ratio (which may result in a higher dermal exposure). 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). The route of exposure may be of importance for the potentially toxic effects of a chemical. In most toxicological studies for regulatory purposes the oral route of administration is used. However, the expected route of exposure of a child should be taken into consideration in the design of toxicological studies since the systemic exposure to a chemical may differ due to different levels of absorption and the absence of a first pass effect following dermal and inhalatory absorption. A further point of concern, for adults as well as children, is the aggregate exposure to a specific chemical from different sources and the cumulative exposure to different substances with the same mechanism of action (e.g. organophosphates and carbamates).

The physiological differences between children and adults may affect the kinetics of a substance in the body, which may render the child less or more susceptible to toxic effects of a chemical. For instance, oral absorption of a substance may be affected by the different gastric pH, gastric emptying rate, concentration of digestive enzymes and gut flora. The high respiratory activity and higher body surface-body weight ratio may increase the relative inhalatory and dermal absorption of substances. The high body water content, the low plasma protein binding capacity and the permeability of the blood brain barrier 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 xenobiotic.

With respect to toxicodynamics, i.e. the interaction between a chemical and the body (organs, tissues) 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 consequenses. 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. The presently used reproduction toxicity tests and the newly introduced neurodevelopmental toxicity test mainly focus on reproductive and neurotoxic effects and are not designed to detect, for instance, immunotoxic effects, effects on lung development or general effects on histopathology or haematology. It is recommended that it is ascertained that, in case of exposure through the milk of the dams, significant quantities of test substance are excreted in the milk. Moreover, since the critical windows in the development of laboratory animals and children are not necessarily the same, the exposure period should be carefully examined.

Since there is a multitude of processes that may differ between children and adults, and the net result of these differences is not clear, at present there is not sufficient information to give a general quantitative statement with respect to differences in vulnerability. For instance, an increased absorption of a substance in a child does not necessarily lead to an increased risk if there is no formation of a toxic metabolite or if there is an increased elimination of the substance. It should be noted that in risk assessment, the use of an intraspecies factor of 10 implies that the 'most sensitive child' is about 10x more sensitive than the 'average' human, and thus that there is a 100-fold variation in susceptibility in the entire human population. In addition, the use of the default assessment factor of 10 for interspecies extrapolation implies that the average human is 10 times more sensitive than the most sensitive animal tested. 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 in order to protect the sensitive groups in the human population, among others children, should always be considered, on a case-by-case basis. For future developments in risk assessment of chemicals with respect to children a number of recommendations are made. For adults as well as children more insight into the specific exposure scenarios is needed. It is proposed to design a decision tree which indicates whether a toxicological data set and the knowledge on the specific exposure are adequate for risk assessment for children. The suitability of young animal toxicity tests should be investigated. A comparison of the dose-response data and the NOAELs of tests in adults and juveniles may provide insight in the range of intraspecies variation with respect to age. Since for pharmaceuticals human data are available it will be worthwhile to follow the developments in the field of kinetics and dynamics of paediatric pharmaceuticals. By using distributions of the physiological and kinetic parameters and PBPK modeling it can be assessed which group of children is most at risk for a certain chemical.

1 Introduction

In regulatory toxicology, recently attention has been focussed on the possible differences between children and adults with respect to their susceptibility to xenobiotics. In order to assess the adverse health effects of xenobiotics a variety of toxicological tests in animals has been developed, among others reproduction toxicity tests. Whereas these tests are generally accepted for hazard identification of prenatal effects, concern has been risen that the toxicological tests presently used may not be adequate to detect some specific effects of perinatal exposure to xenobiotics [1]. It has been shown that there are differences in toxicokinetics and toxicodynamics between the developing animal and the developing child. In addition, the exposure pattern and exposure levels to xenobiotics may also differ between children and adults. The question has arisen whether the present procedures for risk assessment do adequately protect children against adverse effects of chemicals.

In literature the term 'child' may have a dual meaning. On the one hand it may refer to a human being that has not yet reached adolescence. On other occasions the term 'child' is used to identify a specific period in the development of a human being from birth to adulthood. According to the classification by Crom [2] a neonate is less than 1 month of age, an infant is 1 to 23 months of age, a child is 2 to 12 years of age and an adolescent is 13 to 18 years old. In the present report the terms 'child' and 'children' refer to the entire period from birth up to and including adolescence, while the terms neonate and infant refer specifically to the periods in life as described by Crom.

Children may be exposed to toxic substances for longer periods or to higher external doses than adults, because children may spend more time in a room or area in which a toxic chemical is present (e.g. bedroom), are in closer contact with a contaminated surface (e.g. by crawling), display more hand-to-mouth behaviour, and display less hygienic behaviour (e.g. mouthing of objects/surfaces, pica behaviour). In addition, children have a higher body surface to body weight ratio [3] and relatively higher food [1, 4], water [5] and oxygen intakes [3], which may increase their exposure on a body weight basis.

It has become clear from inadvertent exposures that, for certain chemicals, children may be more vulnerable to the toxic effects than adults. This increased vulnerability of children may be the result of differences in toxicokinetics and toxicodynamics. As compared to adults, especially in the early postnatal stages of life marked differences in kinetics and dynamics of substances may exist.
Most data on toxicity of chemicals come from animal studies. Based on the daily dose that causes no adverse effects in the animals, i.e. the No-Observed-Adverse-Effect-Level (NOAEL) an Acceptable Daily Intake (ADI), expressed as mg/kg bw/day, is calculated for humans. To extrapolate the data from the animal studies to the human situation assessment factors are applied. A factor of 10 is used to allow for species differences (4 for toxicokinetics, 2.5 for toxicodynamics) and another factor of 10 is applied to safeguard the variability in the human population (3.2 for toxicokinetics, 3.2 for toxicodynamics)[6].

The concern that children may potentially be at higher risk, due to specific sensitivities and incomplete data with respect to toxicity and exposure led to new legislation in the United States. The Food Quality Protection Act of 1996 [7] requires that '*... an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be*

applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children…'.

In the present report a concise overview of the relevant data from public literature on differences in exposure, and in susceptibility, due to toxicokinetic and -dynamic differences between children and adults is presented. The adequacy of the presently used toxicological tests is discussed and directions for further research are indicated.

2 Exposure

Whether children should be considered as a special sub-population in risk assessment of chemicals should in first instance be based on the exposure profile of children and not on the hazard profile of a chemical (only). Since children have a different dietary pattern, a different activity pattern and behave differently from adults, the exposure pattern and exposure levels of children may substantially differ from that of adults.

2.1 Dietary exposure

Infants may be exposed to xenobiotics through breastfeeding and by consumption of other liquid and solid food products. Children have a higher need for nutrients and a higher caloric demand and hence consume more food and drink more fluids per kg bodyweight than adults. Accordingly their relative exposure to xenobiotics in food is increased. It should be noted that, although children consume the same food products as adults, their dietary pattern is different and less varied [1]. For instance children consume relatively large quantities of dairy products and fruit.

2.2 Other routes of exposure

Apart from exposure to chemicals that are present in food, individuals may be exposed to chemicals through inhalation, dermal exposure or non-dietary oral exposure. As a consequence of their higher inhalatory rate, children have a higher intake of gaseous or airborne chemicals. Also dermal exposure in children may lead to higher systemic levels due to a higher body surface:body weight ratio.
In addition, children may be more exposed to toxic substances than adults because children may spend more time in the same room or area, are in closer contact with a contaminated surface (e.g. by crawling), display more hand-to-mouth behaviour, and display less hygienic behaviour (e.g. mouthing of objects/surfaces, pica behaviour). At the RIVM a consumer exposure model (ConsExpo 3.0) [8] has been developed to estimate exposure levels through inhalatory, dermal and non-dietary oral routes in adults as well as children. Exposure during application (primary exposure) as well as after application (secondary exposure) of a chemical is taken into account.
Specific scenarios for children, especially during the post-application phase, are implemented in ConsExpo. These scenarios use default parameters for e.g. crawling (duration of dermal contact with a surface etc) and hand-to-mouth behaviour that are based on literature data and observational studies.

With respect to testing for regulatory purposes the intended use of the test substance should be taken into account in deciding on the exposure route in the toxicological test. For instance, in case a substance is intended to be vaporised, the developmental effects following inhalatory exposure should be evaluated, since the inhalatory uptake may differ from oral uptake and since there is no first pass elimination in the liver, this might lead to different systemic levels. The same holds true for dermal exposure. Furthermore inhalatory exposure may uncover local developmental effects on the lung.

2.3 Aggregate and cumulative exposure

At present, risk assessment is generally performed for individual substances coming from one source. However, the same substance may be present in a variety of sources, which all contribute to the exposure of an individual, the so-called aggregate exposure. Aggregate exposure is usually referred to as the total exposure of a defined population to a certain chemical from all relevant sources and through all exposure routes [9].
Apart from aggregate exposure to a specific chemical from different sources, it should be noted that often toxic chemicals are part of a certain class of structurally closely related substances which all exert their effect through the same mechanism of action (cumulative exposure). Typical examples of this are classes of pesticides such as organophosphates, pyrethroids and carbamates. Even substances belonging to different classes may affect the same functional target. For instance, both organophosphates and carbamates inhibit cholinesterase activity. The effects of cumulative exposure of adults and children to functionally related substances are largely unknown and, consequently, are not considered in the present risk assessments for regulatory purposes. Although aggregate and cumulative exposure to chemicals is a matter of concern for the entire human population, in view of the differences in exposure characteristics of children compared to adults, this subject needs special attention with respect to children. Especially for substances for which the risk is considered only on a product base for a given application (for instance pesticides), exposure to a given active substance might be much higher due to simultaneous exposure from other sources (e.g. veterinary medicine, biocide, pesticide) that contain the same active substance. In the present regulatory processes these uses are not considered at the same time.

3 Physiology

There is a number of differences in physiology between children and adults. These differences may affect the level of exposure to a chemical, and the kinetics and dynamics of a chemical. Kinetics refers to the processes of absorption, distribution, metabolism of a chemical in the body and excretion from the body. Dynamics describes the interaction between a toxic chemical and the body (tissues, organs, receptors). The most relevant differences with respect to vulnerability and exposure of children to substances are described in table 1.

Table 1. Differences in physiology between children and adults.

Parameter	Difference	ref.
body surface:body weight ratio	About 2.5 times higher in neonates than in adults	3
body water content	About 75 % in neonates, 40-60 % in adults.	10
water intake	About 2-5 times higher in infants *	11
caloric demand	Energy requirement and relative food consumption is 3-4 times higher in infants than in adults *	4
ventilation rate	Volume of inhaled air/kg bw/min is about 3 times higher in neonates than in adults	3
gastric pH	About neutral at birth, shortly thereafter falling to pH 2 (adult value)	12, 13
gastric emptying rate	Irregular at birth, approaching adult values by 6-8 months	14, 15
digestive enzyms	Concentration of digestive enzymes is lower at birth and gradually increases during the first year of life	16
gut flora	Bacterial flora in the intestines is established soon after birth but changes in composition over time	17
brain	Relatively large in children and in development, showing a high rate of tissue proliferation and differentiation. Blood brain barrier is underdeveloped. Brain blood flow increased. Relative high water and low myelin content.	18
liver	Metabolic enzyme system underdeveloped at birth, especially oxidation and glucuronidation processes. Substantial increase within 2-6 months. Adult levels reached within 1-3 years	19
kidney	Renal blood flow and glomerular filtration rate low at birth, reaching adult levels in about 3-5 and 7-12 months respectively.	20, 21
plasma protein (binding)	Plasma protein concentration and binding capacity are lower during the first year of life	20, 21
immune system	High level of tissue proliferation and differentiation	22

* when compared on a body weight basis

An extensive review on the differences in physiology between adults and children, with respect to factors that influence absorption, distribution, metabolism and excretion of xenobiotics, is provided by De Zwart et al. [19].

4 Toxicokinetics

It is known that there are differences between children and adults with respect to the fate of a toxic substance in the body. Especially in the early postnatal stages of life marked differences in the kinetics exist. Recently the age-related differences in kinetics of xenobiotics have been reviewed at RIVM [19]. In the present chapter an overview of the differences between children and adults, based on that RIVM report, is presented. The significance with respect to risk assessment of toxic chemicals is discussed.

4.1 Absorption

Substances may be absorbed through ingestion, inhalation or dermal penetration. For most substances oral ingestion is the predominant route of exposure, however volatile substances may be absorbed mainly by inhalation. For compounds with a $\log P_{ow}$ between –1 and 4 and a molecular weight below 500, the transdermal route of absorption may be of significance.

4.1.1 Oral absorption

Child-specific factors that may influence the absorption of substances are gastric pH, gastric emptying rate, activity of digestive enzymes and the existence and composition of the bacterial gut flora, composition of bile and bile flow. At birth the pH of the stomach in the neonate is about neutral (pH 6-8) but shortly after birth falls to pH 2, which is comparable to adult pH [12, 13]. The neutral pH in neonates will result in a different level of ionisation of toxins as compared to adults, which in turn affects absorption from the gut. The gastric emptying rate is variable and irregular until 6-8 months after birth [14, 15]. The concentration of digestive enzymes is lower at birth and gradually increases during the first year of life [16]. The intestinal wall of neonates is more permeable to macromolecules [19]. The bacterial flora in the intestines is established soon after birth, however, its composition gradually changes over time [17]. All these factors may increase or decrease the absorption of a toxin from the gut.

4.1.2 Inhalatory absorption

Children have a relatively higher caloric demand than adults [4], and consequently a relatively increased respiratory activity [3]. As a consequence, the intake over a certain period of time of an airborne toxin, for instance in the form of a gas, aerosol or dust particle will be increased in children on a body weight basis. In addition, pulmonary function declines with age. Further research is required to establish how the physiological differences in the respiratory system between children and adults affect the absorption of substances.

4.1.3 Dermal absorption

The skin in neonates is immature in comparison to that of adults. For instance, neonates have a higher skin surface pH and skin roughness, a lower hydration of the stratum corneum and

desquamation of the epidermis [23]. However, there are no indications that the dermal absorption of substances in children is substantially different from adults [24].

4.2 Distribution

From a recent publication in which the pharmacokinetic parameters of 45 drugs were compared, it can be concluded that there is a tendency towards larger volumes of distribution of these drugs in children (from neonates up to adults)[25].
The body composition of newborn children differs from that of adults. For instance, the body of neonates contains a higher percentage of water (75 % in neonates vs 40-60% in adults). The body water content is about 63 % in 2 year old infants, and approaches adult values in 12 year old children [10]. The body fat content increases from about 18 % in neonates to 30 % in 1 year old infants, followed by a decrease to 17 % in 15 year old boys. In girls body fat content remains higher. Adult fat content is about 30% in males and 35% in females [19]. Moreover, neonates have a relatively underdeveloped muscular system and the head contributes a large proportion to the body weight. There are some other differences that may be of significance. Firstly, the plasma protein levels and binding capacity are lower in neonates and infants, reaching adult values at about 1 year after birth [20]. This may be of particular importance for exposure to substances that, in the adult, are largely bound to plasma proteins. Generally speaking chemicals that are neutral or hydrophilic or have a low molecular weight are least likely to bind to plasma protein. Since the unbound fraction in the blood determines the degree of distribution to other tissues, a reduction in plasma protein binding may dramatically increase the toxic potential of a substance. On the other hand, lower plasma protein binding may enhance the elimination of a substance.
Secondly, in the neonate the blood brain barrier is immature, which may lead to higher exposure of the brain to hydrophilic xenobiotics, for instance cadmium. The relative size of the brain is larger in children. Moreover the composition of the brain of neonates and children is different from adults. There is less myelin and an increased blood flow in the brain. All these factors may lead to a higher exposure of the brain to toxic substances. This is of particular concern since the brains of neonates and children are still developing and therefore more vulnerable to the toxic effects of substances acting on the nervous system.

4.3 Elimination

A substance may be eliminated from the body through two different processes, metabolic conversion and excretion. Often, excretion of a substance that is rather lipophilic, only occurs after it has been enzymatically converted to more hydrophilic metabolites.

4.3.1 Metabolism

Metabolism of substances serves two purposes. Firstly, by metabolising a substance it often loses its toxic potential, although in certain instances the metabolites are more toxic than the parent compound. Secondly, metabolic processes such as oxidation, glucuronidation, hydroxylation and sulphate conjugation increase the hydrophilicity of the molecule and therefore render it more susceptible to renal excretion. At birth, the liver has an underdeveloped system of metabolic enzymes. Especially oxidation and glucuronic acid conjugation processes are immature in neonates [18, 19, 25]. This means that the rate of detoxification (or activation) and elimination processes in the liver may be less efficient. The

various enzyme systems in the liver mature at different time points. In general, the levels increase substantially within 2-6 months after birth. By 1 to 3 years of age the metabolic potency of the liver approaches adult levels. Although the liver is the major organ for metabolism of xenobiotics, other organs such as the lung, the small intestine and the kidney may also significantly contribute to the metabolic conversion of substances [19]. The metabolic activity of the lung is particularly relevant for substances to which an individual is exposed through the inhalatory route. Human and animal studies have shown that important enzym systems in the lung that are still developing after birth are the cytochrome P450 monooxygenase system, glutathione S-transferases, epoxide hydrolases, superoxide dismutase, catalase and glutathione peroxidase [26].

4.3.2 Excretion

Substances can be excreted through renal excretion, biliary excretion, expiration or perspiration, often after being metabolised. The renal function in the neonate, in particular the renal blood flow and glomerular filtration rate, is low as compared to adults [20, 21], which may lead to a prolonged half-life of the toxin or its metabolites in the blood plasma. In full term neonates renal blood flow and glomerular filtration rate reach adult levels in about 3-5 months and in 7-12 months respectively. Due to the high caloric demand in children their relative respiratory activity is increased. On the one hand, this indicates that in children the relative intake of volatile toxins or toxins in aerosols through inhalation is enhanced, on the other hand the potential to eliminate toxins or their metabolites through expiration will be increased. Little is known about the particularities of biliary excretion of xenobiotics in children.
Experimental research into the pharmacokinetics of drugs has demonstrated that in the early days after birth there may be a decreased elimination of drugs, resulting in a prolonged half life. However, after the neonatal period has passed the elimination of drugs is often enhanced [18, 27]. The same probably is true for non-drug chemicals.

5 Toxicodynamics

The main difference between adults and children with respect to toxicodynamics is the influence that toxic chemicals may exert on the developing organs in young children. The organs in the foetus, but also in the newborn child, undergo cell proliferation (growth), cell differentiation, cell migration, cell maturation, and development of enzyme or receptor systems. Disruption of these processes by toxins may have severe and irreversible consequences. For instance, postnatal exposure to lead induces increased anti-social behaviour and decrements in cognitive function and intelligence, later in life [28, 29]. However, generally speaking little is known at present about the influence of the majority of chemicals on the development of organ systems. In the following sections, the potential effects of chemicals on organ systems in laboratory animals and humans, and the adequacy of the presently used toxicological tests in detecting potential deleterious effects, will be discussed in more detail.

5.1 Development

Exposure to chemicals during the phase that organs develop may have serious effects. Once the organs have developed and enter a phase of growth they are, in general, much less susceptible and effects induced by exogenous substances are often reversible.
With respect to risk assessment, the important question is whether the currently used toxicological tests using laboratory animals are sufficiently sensitive to predict damaging effects of a number of specific toxins on the developing human. The toxicological testing of chemicals in laboratory animals is based on the assumption that the damaging effects of chemicals in the laboratory animal can be extrapolated to humans, and vice versa. From this assumption it follows that most of the development-disrupting effects of chemicals are adequately detected by reproductive and teratogenic tests in laboratory animals, and that these laboratory tests predict the potentially damaging effects of chemicals on children. Although in long-term studies in rats and mice treatment usually already starts when the animals are 6 weeks of age, this is still after the critical period for the development of most organs and organ systems. At present the toxicity of substances in neonates and young animals is tested in reproduction toxicity (OECD guidelines 415 and 416) studies. These studies include postnatal exposure up to the weaning age (OECD415 and the F2 in OECD416) or until adulthood (F1 in OECD416). Before weaning, exposure occurs largely via lactation, although feed consumption increases in the third week before weaning and dietary exposure of pups may occur. These tests allow the study of effects postnatal exposure, especially the F1 generation in OECD416, although at present testing is generally limited to clinical signs, food consumption, weight development and sometimes behavioural testing. Moreover, if there are differences in toxicokinetics, sensitivity of target organs, or period of the development of organs in the mammalian species used for toxicology tests and humans, toxic effects of chemicals that are specific for humans may be overlooked. The brain may be exemplary for this. At birth the development of the brain has further progressed in humans than in rodents. However, in contrast to rodents, where brain development is largely completed at weaning, in the human this organ continues to develop long after birth [30, 31, 32]. Although in studies on reproductive toxicity animals are exposed during the prenatal and postnatal period, the pattern (and level) of exposure in humans may differ, especially in the critical period with respect to brain development

Below, the particularities of the development of certain organ systems in humans, as compared to other mammalians, and the consequences for risk assessment are discussed.

5.1.1 Development of the respiratory tract

The development of the respiratory tract occurs in several phases. In humans, the development of the lungs, in particular of the alveoli, continues well after birth. The development of alveoli even extends into adolescence. In this respect humans differ from rats and mice, in which formation of alveoli occurs during the first 4 weeks after birth. It has been observed that a number of toxins retard lung maturation, decrease the alveolar number and surface area, and impair the function of the lung surfactant system. Little research into the long-term consequences of exposure to these toxins has been performed, although there are indications that the observed functional disturbances may be permanent [26, 33]. More long-term studies are needed, however, to clarify this matter.

5.1.2 Developmental immunotoxicity

Developmental immunotoxicology is still in its infancy. The developing immune system goes through phases of cell production, cell migration through haematopoietic organs, cell-cell interactions, cell differentiation and cell maturation. An overview of the toxic effects of chemicals on the developing immune system has been compiled at RIVM [34]. Disruption of immunodevelopmental processes may have serious consequences, such as long-term or permanent immunosuppression. On the other hand, immune hyper-responsiveness (i.e. allergies) or autoimmune reactions could result from disrupted development of the immune system. Accordingly, the lack of immunological challenge due to increased hygienic standards, and exposure to environmental factors during the development of the immune system have been implicated in autoimmune diseases [35] and atopia and asthma [22, 36]. From animal studies there is evidence that the developing immune system may be not more sensitive to the effects of toxins than the mature immune system, but that the changes in immune function induced by the toxins may be more persistent [37]. However, it has also been reported that perinatal exposure to TCDD reduces vaccination responses and increases the risk of otitis media in Dutch school children [38]. At present, the toxicological tests used for risk assessment are not designed to detect immunodevelopmental disturbances or immunotoxic effects, since immunological parameters are usually not included. It is recommended, however, to amend the current OECD guidelines for developmental and reproductive toxicity testing so that the developing immune system is considered as a potential target of toxicity during developmental stages [39].
In view of the lack in knowledge, further clinical and epidemiological studies are necessary to give more insight in this matter.

5.1.3 Developmental neurotoxicity

The brain, in particular the human brain, is an immensely complex organ, of which the functioning is still poorly understood. It is known that relatively subtle changes in the human brain may alter the mental capabilities or the personality of an individual. A number of psychiatric illnesses, e.g. mental retardation, autism, cerebral palsy, ADHD and schizophrenia, probably have their origin in a disturbed pre-or perinatal brain development. For some of these disturbances the involvement of chemicals has been suggested [40].

In humans, the development of the brain is a process that starts during early pregnancy and continues long after the child is born. Initially the anatomical differentiation of the brain is the most striking feature, but even when all the anatomical structures of the brain are present, functional development still proceeds. Disruption of the anatomical as well as the functional developmental processes may have major consequences.
The brain passes through several stages during development. First there is neurogenesis, i.e. the stage when neurons are formed. This is followed by processes of neuronal migration, outgrowth of dendrites and axons, formation of synaptic connections, development of neurotransmitter systems and receptors, and myelinization.
Although in humans the anatomical development of the brain predominantly occurs before birth, processes such as axon-, dendrite- and synapse formation continue long after birth; some of these processes are not finished before adolescence [31, 32]. The fine-tuning of the interactions between the various brain systems also continues for a long period after birth.
In humans the blood brain barrier is only fully developed from the middle of the first year of life [41]. This means that a chemical such as cadmium, to which the adult blood-brain barrier is impermeable, may well enter the brain in infants. In the rat, it has been reported that exposure to certain pesticides during the development of the blood brain barrier may alter the permeability of this barrier, even for a prolonged time after cessation of the exposure to these pesticides [42].
It is known from animal studies that the developing brain is more susceptible to certain chemicals than the adult brain [3]. It should be noted that substances that are capable of causing disturbances in the developing nervous system are not necessarily neurotoxic in adults. Furthermore, even short periods of exposure to toxic chemicals, such as PCBs, PBDEs and pesticides, may induce long-lasting behavioural disturbances [43, 44].
The risk assessment of neonatal exposure to toxic substances, based on studies using laboratory animals, is hampered by the fact that in certain instances adequate animal models are lacking. Gross abnormalities as a result of neurotoxic damage will probably be detected by studies in animals. However, more subtle, but clinically relevant effects will be difficult to uncover. For instance, learning and memory tasks in animals are probably only sensitive enough to detect relatively large effects on cognitive functioning. Relatively small decreases in cognitive abilities in human individuals, as a result of neurodevelopmental disturbances following exposure to neurotoxins, will be difficult to detect. The possible involvement of neurotoxins in the development of psychiatric disorders will be even harder to detect in animal experiments since many manifestations of these disorders are typical for the human species and are also influenced by life-style and other exogenous factors.
In rats, the major species used for toxicological testing, the brain growth spurt and the anatomical and functional development of the central nervous system occurs for a large part after birth. In the reproduction toxicity tests the dams are treated until weaning. In case the test substance is excreted in substantial amounts in the milk, this test may provide a reliable indication on the neurodevelopmental effects of a substance. However, for substances which are poorly excreted in milk, the reproduction toxicity studies cannot be used to establish neurodevelopmental properties of a substance.
US-EPA has implemented a guideline for developmental neurotoxicity [45] and the draft for a new OECD guideline (426) for the testing of neurodevelopmental toxicity of substances probably will be implemented soon. The developmental neurotoxicity test is aimed at detecting anatomical, histological and functional disturbances induced by interaction of a substance with the developing brain. In principle the guideline proposes to administer the test compound during pregnancy and lactation in the food, however, other means of administration may also be used. In the guideline it is, however, not required to assess the levels of compound in the milk in order to determine whether the pups are actually exposed

after oral administration of the test compound to the mother. Further, if the substance undergoes a high rate of biotransformation, the exposure of the infant through lactation may differ than when directly exposed to the parent compound itself.
In case the level of exposure is too low, the test compound should be administered directly to the pups, provided that stress does not preclude this possibility. The intended use of the test substance may prompt for a different route of exposure. For instance, in case a substance is intended to be vaporised, the developmental effects following inhalatory exposure should be evaluated, since the uptake rate and amount that is absorbed may differ from oral uptake. Since following inhalatory exposure there is no first pass elimination in the liver this may lead to different systemic levels. Furthermore inhalatory exposure may uncover local developmental effects on the lung. For dermal exposure the same reasoning holds true.

5.2 Endocrine disruption

Endocrine disruption is not a specific end point of toxicity but rather 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. In animal studies, effects on morphologic development of the urogenital system may indicate endocrine mechanisms. For example, the uterotrophic assay carried out in immature female rodents assesses weight effects and histological effects on the uterus of substances during a developmental phase when the juvenile uterus is responsive to estrogenic compounds, although at the same time the endogenous production of estrogens is very low. Such a system is more sensitive than the adult uterus, which is already stimulated by endogenous estrogen. However, as yet it is unclear as to when a uterotrophic effect in the juvenile uterus should be considered adverse. At present, various new test systems using young animals are being developed for endocrine disruption, but their role in the risk assessment process has yet to be established. The possible specific relevance of the endocrine disruption issue for children and their development is however beyond dispute.

5.3 Carcinogenicity

Little is known about the specific vulnerability of children to the genotoxic and carcinogenic effects of chemicals. Charnley and Putzrath [46] summarized the results of studies on 30 chemicals in which the effects of age on chemically induced carcinogenesis in rodents were evaluated. Overall, the percentage of studies indicating that young animals were more susceptible than adults (37 %) was about equal to the percentage of studies indicating that young animals were less susceptible than adults (53 %). However, as Landrigan et al. [47] pointed out in a comment, the chemicals included in the studies represent less than 0.2 % of the high production volume chemicals. Moreover, most studies used only one dose level, making it difficult to draw conclusions on differences in sensitivities. Evidently more research is needed in order to gain insight in the relative vulnerability of children to the carcinogenic effects of chemicals.

6 General conclusions

6.1 Exposure

Exposure of children to toxic chemicals may differ substantially from that of adults. As a consequence of their increased metabolic needs, their increased body surface to body weight ratio and their behaviour (e.g. crawling, hand-to-mouth behaviour) the relative exposure (per kg bw) of children to xenobiotics is likely to be higher than that of adults in case of similar external exposure. So, if children are likely to be exposed, it is necessary in the risk assessment for chemicals to perform a separate exposure assessment for children.

6.2 Toxicokinetics and toxicodynamics

It is evident that there are differences between children and adults in the kinetics and dynamics of toxic substances, which may render the child less or more susceptible to the toxic effects of a chemical.
Therefore, in cases where children are likely to be exposed, in addition to the assessment of the specific exposure pattern, also the toxicological profile of a xenobiotic should be carefully examined.
With respect to toxicokinetics, the present data indicate that there are a lot of physiological differences between adults and children, that might result in a different internal dose in children compared to adults. However, it is difficult to predict the overall result of the different processes (for instance: a substance may be more extensively absorbed, but less metabolised to a toxic metabolite, or cleared more rapidly). Therefore, more insight is needed in the differences in toxicokinetic processes between adults and children. One way to study these differences is by using generic PBPK models (see paragraph 6.5).

With respect to toxicodynamics there is evidence that the differences between children and adults may be rather large, especially during early development. The anatomical and functional development of organ systems may render children more sensitive to toxic effects of xenobiotics than adults, which are fully developed. In principal, these effects will be detected in the presently used reproduction and developmental neurotoxicity studies.
It must be kept in mind, however, that the critical windows in the development of laboratory animals and man are not necessarily the same, and therefore, the exposure period should be carefully examined. In addition, special attention should be paid to the route and level of exposure, with regard to extrapolation of results in animal studies to the human situation.
At present, a lot of research with regard to sensitivity of children is going on in the field of pharmaceuticals. Since for the risk-assessment of chemicals in general only information on toxicokinetics and toxicodynamics in laboratory animals is available, it is important to closely follow the developments in the paediatric pharmacology area.

6.3 Adequacy of toxicological tests

It is generally assumed that most of the effects of chemicals on postnatal development are adequately detected by studies on reproductive toxicity and developmental toxicity in laboratory animals, and that these laboratory tests are also predictive for the toxicity of chemicals in children. It should be noted, however, that the presently used toxicity tests focus

on developmental, reproductive and neurotoxic effects, while other parameters (e.g. histopathology, haematology, immunology) in pups are not investigated.
The newly introduced neurodevelopmental toxicity test (OECD 426) may detect effects of substances on the anatomy and function of the brain. However, relatively subtle neurodevelopmental disturbances caused by the test substance may be overlooked, and the usefulness of this test still has to be proven. Also substance-induced neurodevelopmental disturbances underlying typically human psychopathology may not be detected by tests in animals. It should also be noted that the treatment regimen in the test animal might not adequately represent the exposure of the young child. For instance, postnatal exposure of the pup through feeding of the mother will be low for substances that are poorly excreted in milk. Infants and children receive, apart from milk, other solid and liquid foods and may thus be exposed to chemicals via other routes than breast milk. Thus, for substances for which excretion in milk is low the test substance should be administered directly to the pups, providing that stress does not preclude this possibility. For substances to which children are exposed dermally or by inhalation, toxicological tests should use the same administration routes.
Moreover, the presently used protocols for toxicological testing are not adequate for detecting effects of early exposure to substances on carcinogenicity and certain developmental disturbances. For instance, substance-induced disturbances in the immune and endocrine systems may not be uncovered by toxicological tests since no specific tests aimed at detecting disturbances in the functioning of these systems are used. Guidelines to test for (developmental) effects on the immune system are in preparation. The investigation of a broader set of toxicological parameters in the multi-generation toxicity test, especially the parameters that are affected in (sub-)chronic toxicity studies, may provide at least part of the information that is lacking at present.

6.4 Vulnerability of children: Is an additional assessment factor necessary?

From a theoretical point of view it is evident that, due to the complex process of development of organs and organ systems, children may be more vulnerable than adults to the toxic effects of certain chemicals. A typical historical example is the detrimental effect of lead. However, there are not many indications that the current risk assessment procedures do not adequately protect the sensitive groups, such as children, in the human population. There may be several explanations for this:

- The data from the present toxicological tests may be indeed adequate for extrapolation to the human situation, using the present assessment factors.
- An increase in vulnerability due to one factor may be compensated by a reduction in vulnerability due to another factor (for instance, a high absorption of a chemical may be compensated by a high elimination).
- Adverse effects have been identified in epidemiological studies, but an adequate relation to exposure to chemicals may be not clear or proven.
- Adverse effects caused by exposure to chemicals are not identified in epidemiological studies.

At present there is not sufficient information, however, to give a general quantitative statement whether the presently used default assessment factor of 10 for intraspecies variation is adequate to protect children in risk assessment of chemicals. However, in general, the use of an intraspecies factor of 10 implies that the ‘most sensitive child’ is about 10x more

sensitive than the 'average' human, and thus that there is a 100-fold variation in susceptibility in the entire human population. In addition, the use of the default assessment factor of 10 for interspecies extrapolation implies that the average human is 10 times more sensitive than the most sensitive animal tested.
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 in order to protect the sensitive groups in the human population, among others children, should always be considered, on a case-by-case basis.

6.5. Gaps in risk assessment and directions for further research

Exposure
With respect to exposure of children more insight in specific exposure scenarios is needed to get a better estimation of the actual exposure level, especially when it is expected that children might be higher exposed than adults.

- The deviant dietary pattern of children should be taken into account in the exposure assessment. For pesticides this is already common practice, in other frameworks this aspect needs more attention.
- In the exposure assessment, not only point estimates, but also distributions of intake levels should be taken into account in the exposure assessment.
- For the establishment of Maximum Residue Levels the deviant dietary pattern of children should always be taken into account.
- The contribution of the oral, dermal and inhalatory routes of exposure to the total dietary and non-dietary exposure of children should be considered. Because of the different behaviour and physiology of children, both the absolute and the relative contribution of the various routes to the actual exposure will be different compared to adults.
- What are the effects/risks of aggregate exposure to a substance, or the cumulative exposure to substances, either structurally related or from a different chemical class, with a common mechanism of action. Based on the scientific data models for aggregate and cumulative risk assessment should be developed for the population (and thus also for children).

Criteria for the adequacy of the data set: Decision tree.
As mentioned before, the presently used reproduction and developmental neurotoxicity tests will probably detect many of the effects of chemicals on the developing laboratory animal. On the other hand, in the present report a number of situations have been described in which humans differ from laboratory animals and in which toxicological tests in animals are not adequate in detecting adverse effects of substances, such as developmental neurotoxicity or immunotoxicity, on the human child. Thus, it may be concluded that, in view of the potentially increased vulnerability of children, risk assessment of chemicals should be made on a case by case base. We propose that in the near future a decision tree is designed which can be used to assess whether the available toxicological data set is adequate for risk assessment of children.

Suitability of young-animal toxicity tests

The suitability of young-animal toxicity models for extrapolation to the human situation should be investigated. Furthermore, it is interesting to compare the dose-response data and NOAELs of adult test animals to those of juvenile test animals, to gain more insight in the range of intraspecies variation, with respect to age, in a test animal population. However, young animal models will only be relevant in case developing systems are targets for a compound or for its metabolites. Regarding studies in animals this would imply that the choice of an animal model can be better substantiated, leading to a refinement of experiments and a reduction in the number of animals required for testing.

PBPK modeling

It is obvious that the physiology and toxicokinetics in children are different from that in adults. However, it is difficult to get insight in the overall result of the differences, especially in a quantitative sense. A valuable tool in this respect is PBPK- modeling based on the physiology of children. By using distributions of the physiological and kinetic parameters and PBPK modeling it can be assessed which group of children is most at risk for a certain chemical (e.g. lean or fat children).

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