National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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Preliminary study on the added value for human exposure and effect assessment

RIVM Letter report 2016-0215
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Colophon

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Synopsis

Biomonitoring of lead and cadmium
Preliminary study on the added value for human exposure and effect assessment

People are exposed to all kinds of substances (for example via food) , which can be harmful to their health. To accurately estimate the health effects, it is important to determine to what extent these substances actually harm the body. In order to do so it may be helpful to measure concentrations of these substances in body fluids and/or tissues (biomonitoring).

RIVM chose the substances lead and cadmium to investigate to what extent such measurements show a relationship with the exposure as well as the health effects of these substances. RIVM recommends measuring these substances in a Dutch population group. For the purpose of future research it is recommended to study the internal exposure and the effects of lead and cadmium in blood and urine samples of a representative population group.

There were two reasons for choosing lead and cadmium. Firstly, calculations show that for some consumer groups dietary intake may result in values that are close to or slightly above the health based guidance value in question. Secondly, lead and cadmium have one health effect in common: they can both induce kidney damage. Kidney damage can be determined by measuring the presence of certain proteins in urine.

Food is not the only exposure route. Lead and cadmium can be absorbed by the body through several routes: inhalation, ingestion, via the skin or via a combination of these routes. The current approach in the Netherlands is to assess these routes separately, or added together. Using biomonitoring, all relevant routes are assessed simultaneously, providing a more complete picture of the exposure.

Keywords: biomonitoring, lead, cadmium, exposure, health effects

Publiekssamenvatting

Biomonitoring van lood en cadmium
Verkenning naar de toegevoegde waarde voor de beoordeling van humane blootstelling en effect

Mensen staan bloot aan allerlei stoffen, ook via voedsel, die schadelijk kunnen zijn voor hun gezondheid. Om de gezondheidseffecten goed in te kunnen schatten, is het belangrijk te bepalen in hoeverre deze stoffen daadwerkelijk het lichaam schaden. Om dit te kunnen doen kan het helpen om concentraties van deze stoffen in lichaamsvloeistoffen en/of weefsels te meten (biomonitoring).

Het RIVM heeft voor twee stoffen (lood en cadmium) onderzocht in hoeverre dergelijke metingen een relatie laten zien met zowel de blootstelling als de gezondheidseffecten van deze stoffen. Aanbevolen wordt om de onderzochte stoffen in een Nederlandse populatie te gaan meten. Met het oog op toekomstig onderzoek wordt aanbevolen om binnen een representatieve bevolkingsgroep de blootstelling in het lichaam en de effecten van lood en cadmium te bestuderen in bloed- en urinemonsters.

Lood en cadmium zijn om twee redenen gekozen. Als eerste laten berekeningen zien dat sommige groepen mensen lood en cadmium via voedsel kunnen binnenkrijgen in hoeveelheden die dichtbij of net boven de gezondheidsnorm liggen. De tweede reden is dat lood en cadmium één gemeenschappelijk gezondheidseffect hebben: ze kunnen beide de nieren schaden. Eventuele nierschade kan worden gemeten aan de hand van bepaalde eiwitten die aangetoond kunnen worden in urine.

Voedsel is niet de enige blootstellingsroute aan lood en cadmium. De stoffen kunnen via meerdere ‘routes’ tegelijk door het lichaam worden opgenomen: via inademen, inslikken, via de huid of door een combinatie hiervan. Momenteel worden voor de Nederlandse situatie deze routes afzonderlijk geschat of bij elkaar opgeteld. Met behulp van biomonitoring worden alle relevante routes tegelijk meegenomen en dit geeft een vollediger beeld van de blootstelling.

Kernwoorden: biomonitoring, lood, cadmium, blootstelling, gezondheidseffecten

Contents

Summary

In order to properly estimate the health effects of compounds (present in food) in a population, it is important to determine the actual load of the human body to these substances, the so-called body burden. Human biomonitoring (HBM) measures the levels of substances in body fluids and tissues and can be used to study time trends of these levels or to estimate the external and internal exposure of humans to substances. Therefore, HBM can be used to determine or evaluate exposure to these substances in humans. In addition, when internal concentration-effect relations are known, it is also possible to estimate whether adverse effects can be expected in a population. The goal of this desk study is to determine the added value of HBM for human exposure and effect assessment of two candidate substances, namely lead and cadmium.

Lead exposure may cause neurotoxicity, cardiovascular effects and chronic kidney disease in adult humans. Nephrotoxicity is considered the primary effect of cadmium. For both lead and cadmium, recent dietary intake assessments indicate that for some consumer groups dietary intake may result in values that are close to or slightly above the health based guidance value in question. Unfortunately, humans are not only exposed to lead and cadmium via food, but also via other sources, such as smoking cigarettes, breathing air or swallowing dust. Therefore, the dietary exposure only partially contributes to the total body burden of these substances.

In contrast to dietary exposure assessments, biomonitoring data take into account the absorption of a chemical by an individual through all routes of exposure (inhalation, ingestion, absorption through the skin or a combination of these routes) and thus represents the individual's actual exposure level. Furthermore, estimations of the body burden obtained by biomonitoring, can also be used to estimate the risk that certain adverse effects may occur. This is also reflected in the use of two types of biomarkers: biomarkers suitable for exposure assessment and those fit for assessment of health effects. For the assessment of health effects, both the internal concentration of the substance and/or effect-specific biomarkers may be used. In case of multiple route exposure of lead and cadmium, biomonitoring may therefore provide a better estimate of health impact due to lead and cadmium than estimation of a single exposure route.
In this report, an inventory is made of the associations between concentrations of cadmium and lead in biological matrices such as blood or urine and exposure to lead and cadmium. In addition, the associations between cadmium and lead concentrations in biological matrices and observed negative health effects are surveyed. For inorganic lead, the best biomarker is the lead concentration in blood, although urine may be more useful for organic lead. Inorganic lead concentrations in blood (if high enough) are directly correlated to negative health effects. For cadmium, urine is the first choice medium for biomonitoring. Urinary cadmium concentrations (if high enough) are directly correlated to negative health effects. In addition urinary cadmium levels can be linked to several endogenous biomarkers (proteins) that can be used to estimate kidney damage.

Since for lead and cadmium it is known at which body burden adverse effects will start to occur, biomonitoring of these substances may give a more precise indication whether population groups at risk show systemic exposure levels that could result in adverse effects on kidney function. In addition, biomonitoring data may help to determine whether the safety margin used for the calculation of the health based guidance value is sufficient. Furthermore, assuming a large sample size biomonitoring provides a good insight in the interindividual variability in practice.

When sufficient information is available about the relationship between the body burden and the concentration of a substance (or metabolite) in blood or urine or another biological matrix, biomonitoring may be a relatively simple, fast, non-invasive (in the case of urine or hair) and sometimes relatively inexpensive way to measure internal exposure, which can then be used to estimate external exposure and/or effects.

Based on the findings described in this report, it is concluded that cadmium and lead are good candidates for human biomonitoring. It is recommended to determine lead concentrations in blood and cadmium concentrations in urine. Also, good endogenous biomarkers for the determination of kidney damage are available and, in case of cadmium, can be correlated tot urinary cadmium concentrations. For future research, it is recommended to use biomonitoring of lead and cadmium in a sufficiently large population to validate external exposure and to study possible health effects (such as kidney malfunctioning).

1 Introduction

In order to properly estimate the health effects of compounds (present in food) in a population, it is important to determine the actual load of the human body to these substances, the so-called body burden. Often, the dietary exposure of substances is calculated based on concentrations in food products in combination with the consumption amounts and frequencies of these foods. However, the intake provides little information on the actual bioavailability of a substance (and possible toxic metabolites) in the body and says nothing about the ability of this compound to accumulate in the body. Bioavailability and accumulation cannot be estimated (or only poorly) when the toxicokinetics of a substance in laboratory animals and humans differs much. In addition, certain substances (such as environmental contaminants) can also be taken up into the human body through other routes than food. A familiar example is the body burden of lead or cadmium, resulting from intake of these compounds via food, but also via contaminated soil or air.
In practice, blood levels of lead are measured, because it is known at which blood concentrations harmful effects may occur. This is called biomonitoring. Based on the measured blood lead concentrations, the risk on adverse effects can be estimated. In addition, with the aid of kinetic models, the intake can be estimated and compared with the assessment of the dietary intake. Furthermore, for some effects, biomarkers may exist that indicate pathological changes in disease developments.
For this preliminary study the suitability of two possible candidates for human biomonitoring have been selected, namely cadmium and lead. These substances were selected because: 1) recent dietary exposure assessments of cadmium and lead show that some population groups exceed the health-based guidance value, and 2) cadmium and lead have similar negative health effects: sufficient exposure may lead to kidney damage.
In this report, an inventory is made of the associations between concentrations of cadmium and lead in biological matrices such as blood and/or urine, and on the one hand, exposure to lead and cadmium and, on the other hand, observed negative health effects. The results of the inventory will give an indication whether it is possible to use biomonitoring for lead and cadmium to a) estimate whether population groups at risk have biomarker levels that could indicate adverse effects on kidney function and b) estimate whether the safety margin used for the calculation of the health based guidance value is sufficient.
In addition, the possibilities for future research will be discussed, to address which research questions can be answered using biomonitoring.

2 Biological monitoring

Biological monitoring or biomonitoring is an assessment method involving the analysis of blood, urine, hair (or any other body tissue or fluid) or exhaled breath samples, for a hazardous substance or its metabolites. Biomarkers include almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical or biological. Biomarkers may be used in hazard identification, exposure assessment and to associate a response with the probability of a disease outcome (1).
Biomonitoring is often used in the workplace, because for certain chemicals it can provide a more precise estimation of exposure than estimating exposure based on concentrations in workplace air, especially when a substance can be absorbed by multiple routes. Biomonitoring data reflect the total absorption of a chemical by an individual through all routes of exposure (inhalation, ingestion, absorption through the skin or a combination of these routes) and thus represents the individual's actual internal exposure level (2).
However, also outside the workplace, biomonitoring can be useful. In the case that individuals are exposed to a substance via different sources (*e.g.* food, cosmetics, air), biomonitoring can provide a more precise estimation of the body burden than calculations of the concentration of the particular substance in these sources combined with estimated intake or use of these sources. The same is true when information on kinetics of a substance (absorption, (first pass) metabolism, distribution and excretion) is scarce or absent.
Estimations of the body burden, obtained by biomonitoring, can be used to estimate the total exposure of a substance via multiple routes, but also to estimate the risk that certain adverse effects will occur.
Depending on the purpose, different biomarkers may be measured: biomarkers of exposure or biomarkers of effect.

Biomarkers of exposure involve measurements of the parent compound, metabolites or DNA- or protein adducts and reflect internal dose, the biologically effective dose or target dose (3). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. With estimating the exposure, it should be kept in mind that the body burden of a substance may be the result of exposures from more than one source. In addition, depending on the properties of the substance (*e.g.* biological half-life) and exposure conditions (*e.g.* duration, frequency and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. On the other hand, sampling biological fluids on substances that accumulate in the body (e.g. in slowly perfused tissues like bones) may not reflect the actual body burden.
Biomarkers of effects could be changes on a cellular level, such as altered expression of metabolic enzymes but could also include markers for early pathological changes in complex disease developments, such as mutations and preneoplastic lesions (3). This definition encompasses biochemical or cellular signals of tissue dysfunction, as well as physiological signs of dysfunction such as increased blood pressure or

decreased lung capacity. It is noted that these markers are often disease specific, but not substance specific. They also may not be directly adverse, but can indicate potential health impairment (4). To overcome this problem, in many cases, the substance itself or substance-specific metabolites may also be measured in combination with the afore-mentioned markers to check if there is an association.

Currently, one of the main goals of biomonitoring is to identify reference values, which is defined by the German HBM Commission as the 95th percentile of measured concentrations of a substance in the relevant matrix of a reference population (5). For example, such reference values are measured in a long-term biomonitoring project in Flanders, Belgium. In this project, besides reference values for the total population, also reference values for populations 'at risk' are measured, for example for people living in port areas, fruit regions or near incinerators. Repeating such measurements over time has shown certain trends in exposure: the body burden of lead and cadmium of the Flemish population has decreased in the last 10 years, probably partly due to the establishment of a ban on smoking in public buildings and the introduction of unleaded petrol and replacement of lead water pipes. For other exogenous substances, such a trend was not observed (6).
To be able to assess the potential health risks that are associated with the presence of chemicals in a biological matrix, HBM assessment values are useful. Besides HBM assessment values based on human exposure–response data, HBM assessment values in which external dose based guidance values such as tolerable daily intakes have been translated into equivalent biomonitoring levels may also be used (5). The German Human Biomonitorings Commission has established health-related biological exposure limits called HBM values. Two levels were defined: the HBM-I value and the HBM-II value. The HBM-I value is a control value while the HBM-II value is defined as an action level. The HBM-I value describes the concentration of a substance in the body matrix below which, according to the Commission's current assessment, no adverse health effect should be expected. The HBM-II value describes the concentration of a substance in the body matrix above which relevant adverse health effects may occur, and hence immediate action to reduce exposure must be taken and expert care in environmental medicine will be required (5). For example, the HBM-I value for cadmium in urine is 0.5 µg/L for children and adolescents and 1 µg/L for adults, whereas the HBM-II value is 2 µg/L for children and adolescents and 4 µg/L for for adults. For lead in blood, the HBM values have been suspended, because several findings consistently show that no threshold levels can be determined, especially for developmental toxicity in children (7). From the biomonitoring data in Flanders, it was concluded that 11.4% of young people (below 25 years of age) in the reference population, has a urinary cadmium concentration value above 0.5 µg/L but below 2 µg/L (8). Also in DEMOCOPHES, a European project in which 17 countries tested a common approach for human biomonitoring surveys which was developed by COPHES, biomonitoring results of urinary cadmium were compared to HBM values. The P90 of urinary cadmium was below the HBM-I value in both mothers and children that were analyzed (9). In 2015, the European Food Safety Authority (EFSA) published a review of the state of the art of human biomonitoring for chemical substances and its application to human exposure assessment

for food safety (10). In this report, reference values of various chemical substances have been reported for five European countries (not including the Netherlands). The cadmium concentration ranges in blood and urine of non-smoking adults were respectively 0.7-1.4 µg/L and 0.8-1.0 µg/L. The lead concentration range in blood of adults was 19-90 µg/L.
Thus, biomonitoring may be used a) to estimate whether a population is at risk for certain health effects due to exposure to a certain substance, b) as a tool to prioritize for which substances measures should be taken, and c) to monitor if measures taken to reduce exposure are indeed successful.

3 Biomonitoring of lead

3.1 Critical effects

The main target organ for lead toxicity in humans is the central nervous system (CNS). In adults, lead can affect central information processing. Moreover, especially the developing brain is vulnerable to lead-induced neurotoxicity. In children, lowered attention and reaction performance, decreased performance on intelligence tests and impaired cognitive function have been described even at low exposure levels. Chronic lead exposure in adults can also lead to cardiovascular effects, nephrotoxicity, decreased fertility, cataracts, muscle and joint pain. Extreme lead exposure can result in lack of muscular co-ordination, convulsions, and coma (11-13). Furthermore, in 2006, the International Agency for Research on Cancer classified inorganic lead as probably carcinogenic to humans (Group 2A) (14).
Developmental neurotoxicity in young children, cardiovascular effects in adults (elevated systolic blood pressure) and chronic kidney disease in adults (based on a reduction in the glomerular filtration rate (GFR)) have been identified by both EFSA and ATSDR as the most critical effects (11, 15).

3.2 Health-based guidance values

For these critical effects BMDLs based on blood lead levels have been derived by the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) in 2010: a BMDL01 of 12 µg/L (blood level) for developmental neurotoxicity in young children, a BMDL01 of 36 µg/L for cardiovascular effects in adults and a BMDL10 of 15 µg/L for effects on prevalence of chronic kidney disease based on a reduction in the glomerular filtration rate (GFR) to values below 60 mL/min. The CONTAM Panel concluded that the earlier established PTWI of 25 µg/kg bw was no longer appropriate (11).

3.3 Kinetics

Lead enters the body principally through the lungs and the digestive tract where differing amounts from each pathway are absorbed into the bloodstream. Upon entering the bloodstream, it is rapidly transported into the liver, kidney, bone, spleen, lung, heart, and skeletal muscle. The major compartment is bone, which accounts for 70% (children)–90% (adults) of the body burden. The overall distribution of lead appears to be similar in children and adults, although a larger fraction of the lead body burden of adults resides in bone. Lead will accumulate in those regions of bone undergoing the most active calcification at the time of exposure: accumulation occurs predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood. In contrast to lead in bone, which accumulates lead during continued exposure in adulthood, concentrations in soft tissues (e.g. liver and kidney) are relatively constant in adults, reflecting a faster turnover of lead in these tissues compared to bone (11, 15).
Under steady-state conditions, lead in blood is found primarily in the red blood cells (96 to 99%). Most of the lead found in erythrocytes is bound to proteins, the primary binding ligand being the enzyme delta-

aminolevulinic acid dehydratase (ALAD). At blood concentrations <1.92 µM (<400 µg/L), lead levels in whole blood increase linearly with serum levels. At higher blood lead concentrations a non-linear relationship is apparent, and the serum:blood ratio increases dramatically as levels increase, due to saturation of binding in erythrocytes. Approximately 40 to 75% of lead in the plasma is bound to proteins, mainly albumin, though lead also complexes to sulphydryl groups of cysteine, and other ligands, in other proteins.
Blood lead concentrations depend on age and physiological conditions (e.g. pregnancy, menopause, lactation, iron status) and, of course, the extent and frequency of exposure (11, 15).
Elimination is primarily through the kidneys and feces. Sweat, saliva, hair, nails and breast milk are minor routes of excretion. The elimination of lead from both plasma and whole blood varies with level of exposure, sex and age and displays at least two phases. The fast phase reflects the elimination from soft tissues (half-life 20-40 days), the slow one the elimination from the skeleton (half-life 10-30 years) (11, 15)

3.4 Biomarkers of exposure and biomarkers of effect

Lead concentrations in blood, plasma, urine, feces, liver, kidney, hair, and other biological media have been used as biological indicators of exposure to lead. There are no reports regarding biomarkers of effects (e.g. endogenous compounds) specifically for kidney effects, effects on blood pressure, or neurodevelopmental effects. Nevertheless, associations between internal lead concentrations and specific health effects have been observed.

3.4.1 Biomarkers of exposure and associations of lead concentrations with effects

3.4.1.1 Blood

The lead concentration in blood (mainly erythrocyte lead) is a representative of soft tissue lead and reflects, mainly, the exposure history of the previous few months and does not necessarily reflect the total body burden including the much slower elimination kinetics of lead in bone. An important weakness of the use of blood lead is its poor response to changes in exposure at high levels (11, 12, 15). There is saturation with increasing exposure, in particular at blood lead levels above 700 µg/L, but it should also be noted that lead induces anaemia, which will make the use of blood lead problematic, because lead is mainly present in erythrocytes and the volume of which will decrease (16). However, currently, blood is preferred over urine as a biomarker of lead exposure and constitutes the gold standard (17).
Associations of neurotoxic effects with blood lead concentrations in adults have been investigated, however they were not conclusively observed in all studies. Developmental lead neurotoxicity has been reported at exposures that correspond to a blood lead of as low as 20 µg/L. The dose-effect relationship seems to be nonlinear, reflecting a greater relative impact at lower lead concentrations (11, 13).
An inverse association between estimated glomerular filtration rate (GFR), as indicated by decreases in creatinine clearance or increases in serum creatinine concentration, and blood lead has been observed at blood lead levels <50 µg/L in the general population (11).

Meta-analyses of epidemiological findings have found a persistent trend in the data that supports a relatively weak, but significant association between blood lead levels and systolic blood pressure. Quantitatively, this association amounts to an increase in systolic blood pressure of approximately 1 mmHg with each doubling of blood lead concentrations (11).

3.4.1.2 Plasma

The concentration of lead in plasma is very difficult to measure accurately because levels in plasma are near the quantification limits of most analytical techniques and because hemolysis, that occurs with typical analytical practices, can contribute to substantial measurement error. Already a limited erythrocyte hemolysis will shift the metal into the plasma and artificially increase plasma lead levels (11, 12, 15). However, according to Rentschler *et al.*, at high exposure, plasma lead may be a more adequate biomarker of lead exposure and risk than blood lead, because of the saturation that occurs at higher exposure levels. This is in accordance with a closer association between P–Pb and markers of haem synthesis, as compared to B–Pb, especially at high exposure (16).

3.4.1.3 Urine

Urinary lead excretion reflects recent exposure and has therefore limitations for assessing lead body burden. The measurement of lead excreted in urine following an injection (intravenous or intramuscular) of the chelating agent, calcium disodium EDTA (EDTA provocation) has been used to detect elevated body burden of lead in adults and children, and is considered to be a reliable measure of the potentially toxic fraction of the lead body burden (11, 15). However, according to others, urinary excretion of lead after administration of a chelating agent was shown not to be a good measure of total body burden because it mainly reflects lead concentrations in blood and soft tissues and possibly trabecular bone that can be released from these matrices (18). There is an association between lead concentrations in urine and blood, but the variation is too large to allow prediction of an individual blood lead concentration from a urinary lead concentration. In addition, there is an appreciable risk of external contamination during sampling (11) for example via dust, especially considering the sampling method of urine (when compared to blood sampling). No publications were found regarding endogenous biomarkers of effects related to lead exposure that can be measured in urine.

3.4.1.4 Bone

Lead in bone is considered a biomarker of cumulative exposure to lead because lead accumulates in bone over lifetime and most of the lead body burden resides in bone. It should be noted that lead is not distributed uniformly in bone (15). The trabecular bones, such as calcaneus and patella, have a faster turnover than the cortical ones, e.g. tibia. Therefore, the trabecular bones reflect a shorter time-span than the cortical ones and lead levels in cortical bone may be a better indicator of long-term cumulative exposure (15, 18). Lead concentration in bone can be determined in vivo by non-invasive methods based on X-ray fluorescence (detection limit 2 µg/g), but this method is not widely available and primarily used in the research area. Studies suggest that

bone lead levels may be predictors of certain health outcomes, including neurodevelopmental and behavioral outcomes in children and adolescents, and hypertension and decline in renal function in adults (15). Association of neurotoxic effects with tibia lead levels are stronger than with blood lead levels (12).

3.4.1.5 Sweat

Sweat and blood lead concentrations in lead workers were poorly correlated. Sweat has not been widely adopted for monitoring lead exposures (15).

3.4.1.6 Saliva

Studies conducted in rats have found relatively strong correlations between lead concentrations in plasma and saliva (e.g. $r^2>0.9$), compared to blood lead and saliva (15). However, saliva has not been generally accepted as a reliable biomarker of lead exposure because of conflicting and unreliable saliva lead measurements (12).

3.4.1.7 Hair

The use of hair for biomonitoring of lead is not recommended because the method is subject to error from contamination of the hair surface with environmental lead and contaminants in artificial hair treatments, such as dyeing and bleaching (11, 15, 18). Moreover, the concentrations may vary largely, even between different hairs from the same part of the head. Further, the incorporation of lead may vary according to gender and hair color (18). Nevertheless, levels of lead in hair were positively correlated with children's classroom attention deficit behaviour and attention deficit hyperactivity disorder in a study with 277 children (19) and lead in hair was correlated with liver ($rs = 0.51$; $p = 0.003$) and kidney ($rs = 0.57$; $p = 0.001$) lead in a study of deceased smelter workers (20).

3.4.2 Biomarkers of effect

Parameters involved in the haem synthesis process, zinc protoporphyrin (ZPP) and δ-aminolevulinic acid dehydratase (ALAD) activity, are also used to characterize lead exposure status. Several studies have reported that ALAD activity decreased with lead exposure, demonstrating that ALAD activity is one of the most sensitive indicators of lead exposure. ZPP is a normal by-product formed in trace amounts in the final reaction of haem biosynthesis. Increase in ZPP production has long been recognized to be an early biological effect of lead exposure and has been frequently used in health effects monitoring for lead exposure. It is known that ZPP increases after lead exposure and then declines after exposure cessation (21). However, ZPP and ALAD are not lead-specific biomarkers and concentrations can be influenced by many other physiological factors.

3.4.3 Conclusions on biomarkers for exposure and biomarkers for effect

Currently, blood lead concentration is the most widely used and considered to be the most reliable biomarker for general clinical use and public health surveillance. Nevertheless, in some situations other media may be more useful: bone or teeth for past exposures, feces for recent gastrointestinal exposure, or urine for recent organic lead (15). Since associations between lead and critical effects have been studied with

blood lead concentrations (although with varying results), and BDML levels for the critical effects are derived based on blood lead levels, lead concentrations in blood may also be used to estimate the risk of an effect.

3.5 Available kinetic models

Four kinetic models, in particular, are currently being used or are being considered for use in lead risk assessment in humans:

1. the O'Flaherty Model, which simulates lead kinetics from birth through adulthood;
2. the Integrated Exposure Uptake BioKinetic (IEUBK) Model for lead in children developed by EPA;
3. the Leggett Model, which simulates lead kinetics from birth through adulthood;
4. The Carlisle and Wade model, developed by EPA, which has been successfully applied to adults but is less suitable for children

3.5.1 O'Flaherty Model

The O'Flaherty Model is a physiologically based toxicokinetic (PBTK) model for children and adults (see Figure 2).
It simulates lead exposure, uptake, and disposition in humans, from birth through adulthood. Because many of the kinetic functions are based on body weight and age, the model can be used to estimate blood lead concentrations across a broad age range, including infants, children, adolescents, and adults. The model uses physiologically based parameters to describe the volume, composition, and metabolic activity of blood, soft tissues, and bone that determine the disposition of lead in the human body. Lead exchange between blood plasma and bone is simulated as parallel processes occurring in cortical (80% of bone volume) and trabecular bone (20% of bone volume). Uptake and release of lead from trabecular bone and metabolically active cortical bone are functions of bone formation and resorption rates, respectively. Rates of bone formation and resorption are simulated as age-dependent functions, which gives rise to an age-dependence of lead kinetics in bone. The model simulates an age-related transition from immature bone, in which bone turn-over (formation and resorption) rates are relatively high, to mature bone, in which turn-over is relatively slow. Exchanges of lead between blood plasma and soft tissues (e.g., kidney and liver) are represented as flow-limited processes. The model simulates saturable binding of lead in erythrocytes. Excretory routes include kidney to urine and liver to bile. Total excretion (clearance from plasma attributable to bile and urine) is simulated as a function of glomerular filtration rate. Biliary and urinary excretory rates are proportioned as 70 and 30% of the total plasma clearance, respectively. Several variants of this physiologically based model exist: for the human, the rat, and the cynomolgus monkey (15, 22, 23).
A subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability in exposure, absorption, and erythrocyte lead binding capacity. This extension of the model can be used to predict the probability that children exposed to lead in environmental media will have blood lead concentrations exceeding a health-based level of concern (e.g., 10 µg/dL) (24).

Timchalk et al. adapted the O'Flaherty model for lead analysis in saliva (25).

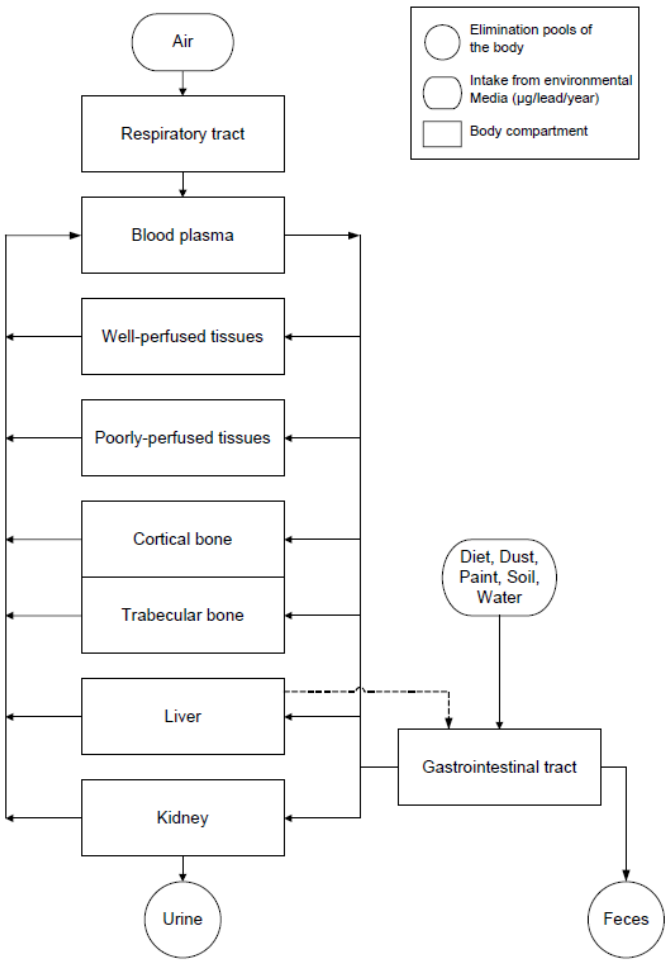

Figure 2. Schematic model for lead kinetics in which lead distribution is represented by flows from blood plasma to liver, kidney, richly-perfused tissues, poorly-perfused tissues, and cortical and trabecular bone (15).

3.5.2 *Integrated Exposure Uptake Biokinetic (IEUBK) Model*

The IEUBK Model for Lead in Children (see Figure 3) is the most widely validated exposure assessment model. It has also been used by EFSA (11). It is a classic multicompartmental model linked to an exposure and probabilistic model of blood lead distributions in populations of children 0 to 7 years. The model has four major submodels:

1. an exposure model, in which average daily intakes of lead (µg/day) are calculated for exposure concentration of lead in air, diet, dust, soil, and water;
2. an uptake model, which converts environmental media-specific lead intake rates calculated from the exposure model into a media-specific time-averaged uptake rate (µg/day) of lead to the central compartment (blood plasma);
3. a biokinetic model, which simulates the transfer of absorbed lead between blood and other body tissues, elimination of lead from the body (via urine, feces, skin, hair, and nails), and predicts an

average blood lead concentration for the exposure time period of interest; and

4. a blood lead probability model, which applies a log-normal distribution (with parameters geometric mean and geometric standard deviation) to predict probabilities for the occurrence of a specified given blood lead concentration in a population of similarly exposed children.

The biokinetic component includes a central compartment, six peripheral body compartments, and three elimination pools. The body compartments include plasma and extra cellular fluid (central compartment), kidney, liver, trabecular bone, cortical bone, and other soft tissue. The model simulates growth of the body and tissues, compartment volumes, and lead masses and concentrations in each compartment. Exchanges between the central compartment and tissue compartments are simulated as first-order processes, which are parameterized with unidirectional, first-order rate constants. Bone is simulated as two compartments: a relatively fast trabecular bone compartment (representing 20% of bone volume) and a relatively slow cortical bone compartment (representing 80% of the bone volume). Saturable uptake of lead into erythrocytes is simulated, with a maximum erythrocyte lead concentration of 120 µg/L. Excretory routes simulated include urine, from the central compartment; bile-feces, from the liver; and a lumped excretory pathway represented losses from skin, hair and nail, from the other soft tissue compartment (11, 15).

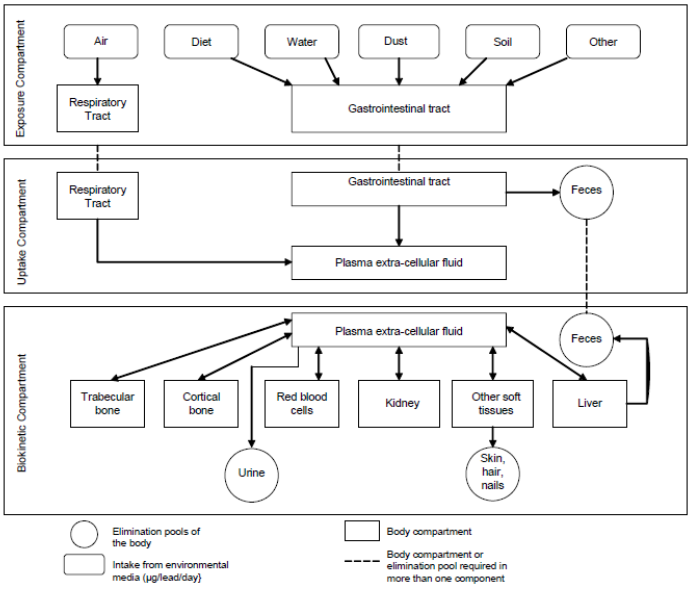

Figure 3. Schematic for integrated lead-exposure-kinetics model in which simulated multi-media exposures are linked to simulations of lead uptake, tissue distribution and excretion (15).

3.5.3 Leggett model

The Leggett Model (see Figure 4) is a classical multicompartmental kinetic model of lead uptake and disposition in children and adults. It was originally developed for the International Commission on Radiological Protection (ICRP) as part of a set of biokinetic models for "bone-volume-seeking" or "calciumlike" elements. The model includes a

description of circulating lead, a concentration-dependent transfer rate into red blood cells (provided the lead concentration in red blood cells exceeds a specified threshold level), and consideration of the brain as a separate compartment. The model describes the age- and time-dependent distribution and excretion of lead that has been injected or absorbed into blood. The Leggett Model includes a central compartment, 15 peripheral body compartments, and 3 elimination pools. The transport of lead between compartments follows first-order kinetics provided the concentration in red blood cells (RBCs) stays below a particular concentration. When the concentration in RBCs exceeds that concentration, the transfer rate from diffusible plasma to RBCs is assumed to decrease as the concentration in RBCs increases. At the same time, the deposition fractions in other compartments are increased due to decreased competition from the RBCs, but first-order transport between all other compartments is assumed to be maintained at all levels of exposure. A concentration of 60 pg/dL RBC (corresponding to a blood lead concentration of about 25 pg/dL) is assigned as default value, but the actual concentration may vary substantially from one person to another and may also depend on the duration of exposure. A particularly important advantage of the Leggett model is that age-dependent parameter values are provided for young, middle-aged, and older adults as well as for infants, children, and adolescents. A second important advantage is that the user has versatile and nearly complete access to almost all model input and output parameters (26, 27).

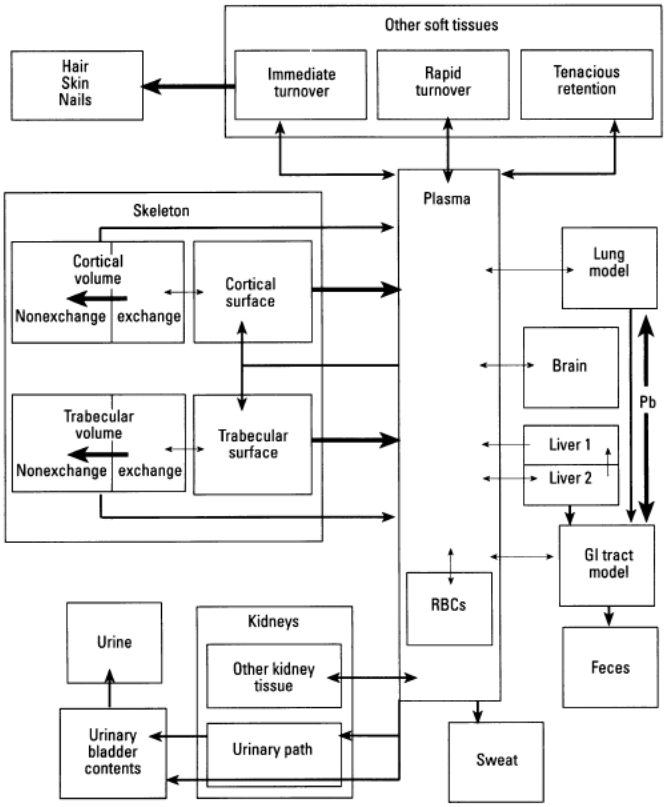

Figure 4. Structure of the Legett/ICRP biokinetic model for lead showing the compartments and direction of lead movement between compartments (27).

The Office of Environmental Health Hazard Assessment (OEHHA) adjusted the Leggett model to make it suitable for workplace exposure scenarios. They modified the Leggett model by

1. adjusting bone, urine clearance, and blood parameters to improve the fit of the model to observed data;
2. assuming a time-weighted average breathing rate of 26 m^3/day, which reflects time-weighted breathing rates based on assumed activity levels for workplace and non-workplace exposure to airborne lead; and
3. setting a default value of 30% for transfer of inhaled lead to blood ("inhalation transfer coefficient") for particles in the size range found in industrial settings (28).

3.5.4 The Carlisle and Wade model

The Carlisle and Wade model, used by the California EPA, considers lead from dietary, drinking water, soil and dust and an empirically determined pathway-specific factor that reflects the ratio between lead intake and B-Pb. The model estimates B-Pb using exposure from dietary and non-dietary sources, their corresponding medium-specific contact rates and an empirically determined ratio between intake and blood level (11). Unfortunately, no figure depicting the model could be found.

3.5.5 Conclusion on models

Because of their robustness and suitability, EFSA has used both the IEUBK model for children and the Carlisle and Wade model for adults for the estimation of blood lead levels from dietary and non-dietary exposure. Although it is the most widely validated exposure assessment model, the IEUBK model is developed for children up to 7 years. It is therefore not useful for the assessment of exposure levels that cause kidney effects in adults. The Carlisle and Wade model, however, has been successfully been applied to adults and the BMDL for renal effects established by EFSA has been determined using this model. Therefore, this model seems the most suitable when we want to further examine the relation between lead body burden and renal effects in the Dutch population.

4 Biomonitoring of Cadmium

4.1 Critical effects

Cadmium is primarily toxic to the kidney, especially to the proximal tubular cells where it accumulates over time in the epithelial cells, resulting in a generalized reabsorptive dysfunction that is characterized by polyuria, glucosuria and low molecular weight proteinuria (4, 29-31). The earliest sign of tubular toxicity is a decreased tubular reabsorption, resulting in an increased excretion of low molecular weight proteins (particularly β2-microglobulin, α1-microglobulin, and retinol binding protein), increased urinary levels of intracellular enzymes such as N-acetyl-β-glucosaminidase (NAG); and increased excretion of calcium and metallothione. At higher exposure levels, the tubular damage may progress to decreased glomerular filtration rate, and eventually to renal failure (4, 31).
Recent studies have highlighted the fact that adverse renal effects of cadmium may result from even low levels of exposure and that women, children and individuals with confounding health conditions, such as diabetes, may be especially susceptible. Impaired renal tubular reabsorptive function has been shown when urinary cadmium concentration exceeds 4 µg/g creatinine (29, 30).
Cadmium can also cause bone demineralisation, either through direct bone damage or indirectly as a result of renal dysfunction. The adverse effects of cadmium on bone were first recognized in a severe bone disorder known as Itai-itai disease (31).
Furthermore, the International Agency for Research on Cancer has classified cadmium as a human carcinogen (Group 1) on the basis of occupational studies. Newer data on human exposure to cadmium in the general population have been statistically associated with increased risk of cancer such as in the lung, endometrium, bladder, and breast (29, 31). Cadmium is not directly genotoxic. Two mechanisms play an important role in cadmium genotoxicity: 1) induction of reactive oxygen species (ROS) and 2) inhibition of DNA repair (31).

4.2 Health based guidance values

The Scientific Panel on Contaminants in the Food Chain (CONTAM) selected a reference point of 1 µg urinary cadmium/g creatinine for risk evaluation. This was based on an overall group-based BMDL, corresponding to 5% extra risk of kidney dysfunction of 4 µg urinary cadmium/g creatinine that after adjustment by a calculated chemical specific adjustment factor of 3.9 to account for inter-individual variation of urinary cadmium within the study populations, led to the value of 1 µg urinary cadmium/g creatinine) (31).
The dietary cadmium exposure that corresponded to the urinary cadmium concentration of 1 µg/g creatinine was estimated by one-compartment modelling of the data from 680 women with no smoking history, aged from 56 to 70 years. In order to remain below 1 µg cadmium/g creatinine in urine in 95% of the population, the long term daily dietary cadmium exposure should not exceed 0.36 µg Cd/kg bw. Because of the long half-live of cadmium in the human body a health based guidance value should be set on a weekly rather than a daily

basis. Therefore, the CONTAM Panel established a tolerable weekly intake (TWI) of 2.5 µg/kg bw. Subgroups of the population (vegetarians, children, smokers and people living in highly contaminated areas) may exceed the TWI by about 2-fold (31).

4.3 Kinetics

Cadmium absorption after dietary exposure in humans is relatively low (3–10%), whereas cadmium is very efficiently absorbed from the lung; up to 40–60% of inhaled cadmium reaches the systemic circulation. This is particularly important for smokers because (high) cadmium levels can be found in tobacco.
Gastrointestinal bioavailability is dependent on the source of cadmium and the physiological state of the organism: it is substantially higher in individuals with low body stores of iron and it is generally higher in women than in men (4, 29-31). Gastrointestinal uptake of cadmium is a saturable process with fractional absorption decreasing at high concentrations (31).
Cadmium widely distributes throughout the body, with the highest concentrations found in the liver and kidney. Liver and kidney cadmium concentrations are comparable after short-term exposure, but the kidney concentration exceeds the liver concentration following prolonged exposure. In humans, subjected to normal low-level exposures, approximately 50% of the total cadmium body burden is found in the kidney and 15% in the liver, and only a relatively small part is stored in bone (4, 29, 31).
In the blood, cadmium is mainly found in the erythrocytes, only a small percentage (<10%) remains in the plasma. Cadmium in blood is bound to albumin and metallothionein. Because of the high affinity of cadmium for metallothionein, cadmium that is bound to metallothionein is not available for uptake by most tissues. The small cadmium-metallothionein complex is filtered in the renal glomerulus, reabsorbed in the tubular cells, and accumulated in the kidney (29-31).
Cadmium is efficiently retained in the kidney and liver in the human body, with a very long biological half-life ranging from 10 to 30 years. Daily fecal and urinary excretions are estimated to represent 0.007 and 0.009 % of body burden, respectively (4, 31).

4.4 Biomarkers of exposure and biomarkers of effect

Cadmium levels in blood, urine, feces, liver, kidney, hair, and other tissues have been used as biological indicators of exposure to cadmium. In addition, several endogenous biomarkers of kidney effects have been used.

4.4.1 Biomarkers of exposure and associations of cadmium concentrations with effects

4.4.1.1 Blood

Blood cadmium is considered the most valid marker of recent exposure and is usually assessed in whole blood. To control for variability in hematocrit levels, the whole blood cadmium should be adjusted to the hemoglobin concentration (4, 31). While blood levels of cadmium can yield information regarding recent exposures, they often do not provide information regarding the total body burden of cadmium or the severity

of injury in specific target organs (30). However, they are also considered a useful measure of long-term exposure in subjects without exposures other than dietary especially among non-smokers. Blood cadmium correlates closely with urinary cadmium (31).
Based on data from three areas in China, a marked dose-response relationship between blood cadmium and the prevalence of renal dysfunction (using effect biomarkers of renal dysfunction, such as β2-microglobulin, retinol binding protein and albumin) was demonstrated. The number of abnormalities in kidney was related to the level of cadmium exposure (32).

4.4.1.2 Urine

Cadmium levels in urine are widely accepted as a measure of the body burden and the cumulative amount in the kidneys. Urine cadmium levels primarily reflect total body burden of cadmium, although urine levels do respond to recent exposure (4, 31). However, with low, or even moderate levels of exposure (not further specified), any cadmium that is filtered at the glomerulus is almost completely reabsorbed by epithelial cells of the proximal tubule; little or no cadmium is excreted in the urine. It is only when the body burden of cadmium is fairly large (not further specified) and/or kidney injury begins to appear that urinary excretion of cadmium increases significantly (30). When the critical level for renal damage has been reached (impaired renal tubular absorption has been shown at levels of 4 µg Cd/g creatinine (29, 30)), urinary cadmium levels rise sharply because of the release of intrarenal cadmium along with decreased renal reabsorption of cadmium. Among environmentally exposed subjects, there was good agreement between urinary cadmium levels measured at different times, suggesting that a single determination could be an accurate measure (4).
However, ideally, 24h urinary excretion should be used, although studies have shown a close relationship between urinary 24h cadmium excretion and cadmium measured in spot urine samples. As for all biomarkers in spot urine, the urinary cadmium concentration needs to be adjusted for dilution (29, 31). However, it is noted that a significant circadian rhythm in urinary cadmium excretion over 24h was observed: significantly higher in the second morning sample (09:30) and significantly lower in the afternoon samples (14:30, 17:30 and 22:00) compared to overnight samples (29).
Reviews of the existing data (occupational and environmental exposure) show that a urinary cadmium concentration of 2.5 µg/g creatinine corresponds to a kidney cadmium concentration of about 50 µg/g (29, 31).
Caution is needed if urinary cadmium is used as a biomarker of exposure when studying renal effects of cadmium toxicity at low-level cadmium exposures. Studies that have used urinary cadmium as a biomarker for cadmium exposure, when studying kidney effects, might have overestimated the risk of kidney effects from cadmium toxicity at low cadmium exposures (29).
As was observed for blood cadmium, a marked dose-response relationship between urinary cadmium and the prevalence of renal dysfunction (using effect biomarkers of renal dysfunction, such as β2-microglobulin, retinol binding protein and albumin) was demonstrated based on data from three areas in China. The number of abnormalities in kidney was related to the level of cadmium exposure (32).

4.4.1.3 Feces

Fecal cadmium primarily reflects recently ingested cadmium and, therefore, is not a good indicator of long-term cadmium exposure. It may however be used as a direct indicator of daily dietary intake of cadmium because dietary cadmium is poorly absorbed in the gastrointestinal tract (4).

4.4.1.4 Liver and kidney

Liver and kidney tissues preferentially accumulate cadmium, and concentrations of cadmium in liver and kidney may be measured using non-invasive techniques such as in vivo neutron activation analysis or in the kidney by X-ray fluorescence analysis; however, the limit of detection is near background levels (not further specified). In addition, it is too expensive for routine monitoring (4, 33).

4.4.1.5 Hair

Hair levels of cadmium have been used as a measure of cadmium exposure, although the possibility of exogenous contamination has led to substantial controversy concerning the reliability of hair levels as a measure of absorbed dose. It was concluded that cadmium hair analysis was a reliable indicator for the subjects with the highest exposure, but was not sensitive enough to resolve differences for low level exposures (4).

4.4.2 Biomarkers of effect

Besides levels of cadmium in blood, urine or kidney, several biomarkers of cadmium effects are used. The level of metallothionein gene expression was significantly correlated with blood and urinary cadmium levels (4).

These markers are associated with several stages of the development of renal dysfunction (see Figure 5). Urinary markers of (cadmium) nephrotoxicity can be classified into 3 broad categories: (i) cadmium and cadmium-binding proteins; (ii) low molecular weight proteins; and (iii) proteins and enzymes derived from the brush border, intracellular organelles or the cytosol of proximal tubule epithelial cells (30).

i. Under normal conditions, circulating cadmium, which is bound to low molecular weight molecules such as metallothionein, cysteine or glutathione, is filtered at the glomerulus and taken up by the epithelial cells of the proximal tubule. During these early stages of exposure only extremely small amounts are excreted in the urine. During this stage of exposure, the presence of cadmium or metallothionein in the urine most likely results from the normal turnover and shedding of epithelial cells and is a reflection of the level of cadmium exposure and the body burden of cadmium. However, over time, the concentration of cadmium in the epithelial cells increases to the point that cadmium disrupts tubular reabsorptive processes. At this stage, the excretion of cadmium and metallothionein begin to increase in a more or less linear manner. As the intracellular levels of cadmium increase further, more of the epithelial cells begin to die and slough off. At this point, the urinary excretion of cadmium and metallothionein increase markedly. The blood levels of cadmium in nonexposed populations are typically less than 0.5 µg/L. Blood levels higher than 1.0 µg/L are generally indicative of cadmium exposure;

levels higher than 5 µg/L are considered hazardous. Urinary levels of cadmium in non-exposed populations are usually below 0.5 µg/g creatinine; values above 1–2 µg/g are indicative of exposure or elevated body burden. The critical urinary cadmium concentration that is associated with the onset of renal injury is usually about 2–10 µg/g creatinine, which corresponds to a renal cortical cadmium concentration of about 150–200 µg/g tissue. However, there is significant evidence that even lower urinary levels of cadmium may be associated with adverse effects. For metallothionein, the critical urinary level that is associated with the onset of overt kidney injury is approximately 300 µg metallothionein/g creatinine (30).

ii. Renal dysfunction, usually first manifested as impaired tubular reabsorption of filtered solutes (such as low molecular weight proteins), is generally considered the primary toxic effect of chronic cadmium exposure. Under normal circumstances, these filtered proteins are efficiently reabsorbed by the proximal tubule and are not excreted to any great extent in the urine. However, as cadmium accumulates in the proximal tubule, absorption of these proteins becomes impaired and the proteins begin to appear in the urine. Of these proteins, β2-microglobin has been most widely employed as a standard marker for monitoring for the early stages of cadmium exposure and toxicity. It is also the only marker currently in use that has been related to severity of tubular dysfunction, in the absence of other disease conditions. Even though β2-microglobulin has proven to be a very useful biomarker, its lack of stability in acidic urine can be problematic. There is a need to control the pH of samples to prevent its degradation, although it is also possible that degradation may occur already in the bladder.
Also increased levels of retinal binding protein (RBP) are suggestive of impairment of tubular reabsorptive function. Unlike β2-microglobulin, however, RBP is stable in acidic urine and no special preservative or alkaline treatment is required.
Urinary alpha-1-microglobulin (A1M), also called human complex-forming glycoprotein (pHC) is another sensitive marker of tubular renal dysfunction. As with retinol binding protein, A1M is more stable in urine than β2-microglobulin at room temperature and low urinary pH levels.
For all these markers, it should be noted that tubular renal dysfunction can be caused by exposures and diseases other than cadmium, so they are not specific markers of cadmium-induced effects. For example, urinary ß2-microglobulin excretion generally rises with age and may be affected by overload proteinuria or competition for tubular uptake at the tubular reabsorption sites (4, 30, 31).

iii. The appearance of enzymes like N-acetyl-b-D-glucosamidase (NAG), lactate dehydrogenase (LDH), alkaline phosphatase, and more recently, alphaglutathione-S-transferase (a-GST) in urine is classically thought to result from the leakage of intracellular contents when necrotic proximal tubule epithelial cells lose their membrane integrity and/or slough off into the urine. However, results of recent studies indicate that at the time the cadmium induced increase in the urinary excretion of a-GST and LDH

occurs, there is little evidence of necrosis in the proximal tubule. Enzymes such as NAG, a-GST and LDH are attractive urinary markers because even low levels can be detected with relatively simple assays. On the other hand, enzymes can be subject to inhibition/interference with many exogenous substances. NAG, a lysosomal enzyme present in high concentrations in the proximal tubule, has been shown to correlate with urinary cadmium levels in occupationally and environmentally exposed subjects and has a better correlation with urinary cadmium levels than β2-microglobulin at low cadmium exposure levels (urinary cadmium <10 µg/g creatinine). Increased NAG activity can result from effects other than renal damage.
One of the more promising urinary markers that have been described recently is kidney injury molecule-1 (Kim-1). Kim-1 is a transmembrane protein that is not detectable in normal kidney but is expressed at high levels in the proximal tubule after ischemic or toxic injury (More details in (30)) (4, 30, 31).

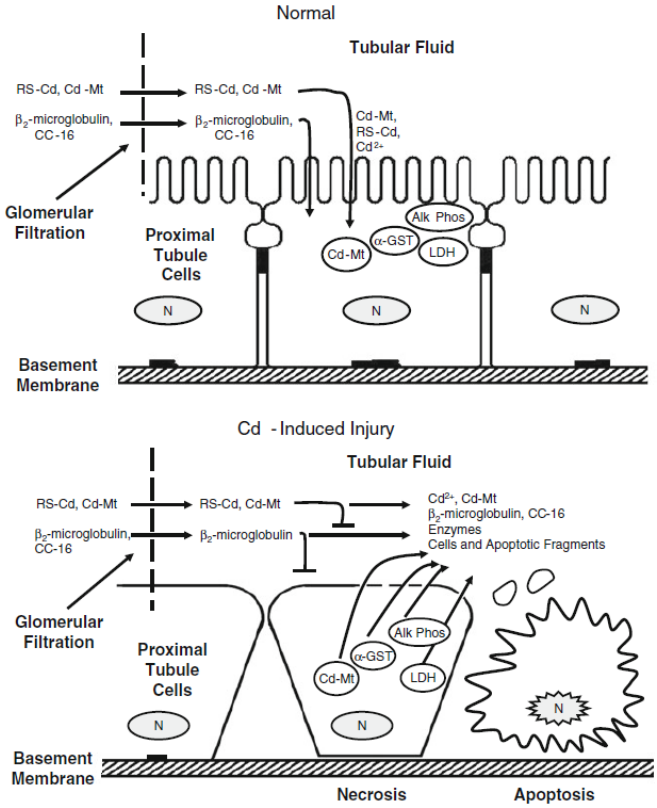

Figure 5. Mechanistic origins of classic biomarkers of cadmium nephrotoxicity (30).

4.4.3 *Conclusions on biomarkers for exposure and biomarkers for effect*

The best biomarker for exposure is cadmium in urine. At the present time, there is no single biological indicator for cadmium toxicity that is entirely adequate when considered alone. Measurement of cadmium levels in various biological materials can provide an indication of recent or total cadmium exposure, but the probability of adverse effects cannot be reliably predicted. For the early stages of renal dysfunction, β2-microglobin in urine is still the standard marker, also because it is the

only marker that has been related to severity of tubular dysfunction, in the absence of other disease conditions. In addition, the BMDL for cadmium-induced tubular effects, as established by EFSA, is based on β2-microglobin in urine (31). Nevertheless, urinary RBP and A1M could also be used as biomarkers for cadmium induced effects. In practice, low albumin levels in urine (microalbuminuria) can be used as biomarker of tubular damage (personal communication with Prof. dr. S.J.L. Bakker, nephrologist at the University of Groningen). A new biomarker of kidney function is a protein called cystatin C. In combination with creatinine it can be used for the early detection of kidney dysfunction (personal communication, S. Bakker).
The selection of an endogenous biomarker may depend on the costs and availability of the assays. In addition, it is possible that in certain cohort studies, results on one of the markers are already available.
Measurement of such markers of renal dysfunction can provide a sensitive measure of early kidney toxicity, but cannot establish whether cadmium exposure was the cause (4). Therefore, a combination of the endogenous biomarkers of renal dysfunction mentioned above and chemical analysis of cadmium with a sufficiently sensitive method seems to be the preferred approach.

4.5 Available kinetic models

According to EFSA and ATSDR, The Nordberg-Kjellström model provides the best overall description of cadmium toxicokinetics. In addition, it is the only model which is largely based on human data (4, 31).

4.5.1 Nordberg-Kjellström model

The Nordberg-Kjellström model (see Figure 6) is a linear eight-compartment model that describes the disposition of cadmium via the oral and inhalation routes of exposure only. By either route of exposure, the model assumes that cadmium enters into any of three blood compartments (plasma, erythrocytes or bound to metallothionein). The model does not take into account induction of metallothionein after cadmium exposure. From the blood, cadmium is calculated to distribute to either the liver, kidney, or "other tissues," the major accumulation sites. Elimination is either via the feces or in the urine. The transport of cadmium between the compartments is assumed to follow first-order exponential functions and is driven on concentration-dependent gradients. The flow of cadmium between the compartments was generally assumed to follow first-order exponential functions. The 21 distribution coefficients were estimated by fitting the calculated cadmium concentrations in kidney, liver, urine, blood, and other tissues to the observed concentrations for Swedes with different smoking habits and with and without occupational cadmium exposure. Coefficients for the flow of cadmium were estimated from empirical data both from animals and man (34, 35). The Nordberg-Kjellström model was validated using several independent sets of human data from both Sweden and Japan (4).
Limitations of the model are:

1. the linear nature of the model may not adequately allow a good description of known nonlinearities in biological responses to cadmium dosing, and

2. the phenomenological approach taken with this model does not provide a foundation for incorporating biological variability into the model parameters (15).

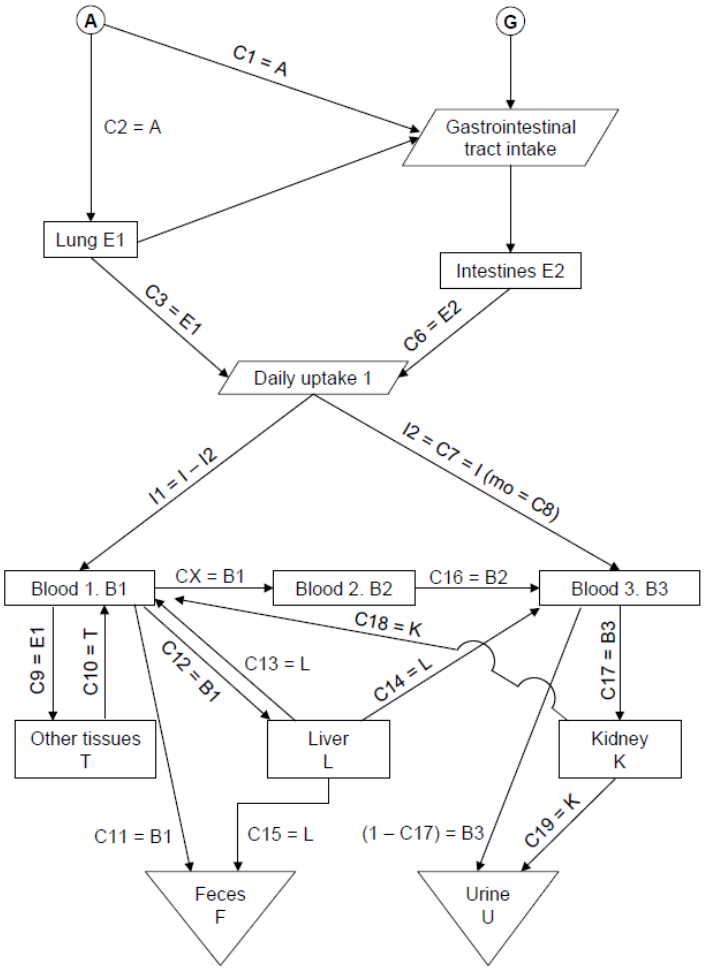

Figure 6. A schematic representation of the Nordberg-Kjellström model (4).

4.5.2 *Adaptations to the Nordberg-Kjellström model*

The Cadmium Dietary Exposure Model (CDEM) utilizes national survey data on food cadmium concentrations and food consumption patterns to estimate dietary intakes in the U.S. population. The CDEM has been linked to a modification of the cadmium biokinetic model of Kjellström and Nordlberg to derive predictions of kidney and urinary cadmium that reflect U.S. dietary cadmium intake and related variability. The model describes the cadmium toxicokinetic as the Nordberg–Kjellström model with some modifications, such as the use of differential equations to describe the intercompartmental transfers of cadmium and the growth algorithms for males and females and corresponding organ weights which are used to calculate age-specific cadmium concentrations from tissue cadmium burdens. Variability in dietary cadmium intake was propagated through the Nordberg-Kjellström model using a Monte Carlo approach (36, 37).
The Nordberg–Kjellström model was modified by Hwan et al. according to parameters for Koreans (38).

Fransson et al combined the Nordberg–Kjellström model for cadmium with a data set from healthy kidney donors to re-estimate the model parameters to improve the model (39).
Ju et al modified the Nordberg–Kjellström model to estimate the cadmium distributions through both inhalation and seafood consumption exposures. A Hill-based dose–response model was used to assess human renal dysfunction and peripheral arterial disease risks for long-term cadmium exposure (40).

4.5.3 Conclusion models

Currently, the Nordberg-Kjellström model is the most commonly used model for cadmium risk assessment work. It has already been used to assess renal dysfunction in humans. Therefore, it seems perfect to be used in the assessment of cadmium-induced kidney effects in the Dutch population.

5 Research implications for biomonitoring

In young children, developmental neurotoxicity is considered to be the most critical effect of lead exposure (BMDL01 of 12 µg lead/L blood). Although the central nervous system is also a target in adults, cardiovascular effects (BMDL01 of 36 µg lead/L blood) and especially chronic kidney disease (BMDL10 of 15 µg lead/L blood) are the main effects. For inorganic lead exposure, the lead concentration in blood is the best biomarker for exposure. Concentrations in blood also correlate with kidney effects, and therefore lead blood may also be used to estimate the risk of kidney damage.
Based on dietary exposure assessment, it can be concluded that an adverse effect from lead in some consumers, particularly in children from 1-7 years of age, cannot be excluded (11, 41). However, humans are not only exposed to lead via food. It is therefore important to apply biomonitoring to be able to take the exposure to lead from other sources into account and to get a realistic overview of the population's total exposure.

Due to the accumulation of cadmium in epithelial cells of the proximal tubule, nephrotoxicity is considered the primary effect of cadmium. The effects of cadmium on the kidney and the progression of kidney failure are very well described. For cadmium, urine has been accepted as first choice medium for biomonitoring. Although ideally 24 hour urine should be used, a relationship between urinary 24h cadmium excretion and cadmium measured in spot urine samples has been shown. However, with low, or even moderate levels of exposure, any cadmium that is filtered at the glomerulus is almost completely reabsorbed by epithelial cells of the proximal tubule and little or no cadmium is excreted in the urine. Urinary excretion of cadmium starts to increase significantly only when the body burden of cadmium is fairly large (not further specified). The critical urinary cadmium concentration that is associated with the onset of renal injury is usually about 2–10 µg Cd/g creatinine, although there is evidence that adverse effects may occur at even lower urinary levels of cadmium (30). Besides measuring cadmium itself in urine, several endogenous biomarkers of cadmium exposure can be used. Of these effect biomarkers, ß2-microglobin has been most widely employed as a standard marker for monitoring of the early stages of cadmium exposure and toxicity. However, its lack of stability in acidic urine can be problematic. As an alternative, other proteins (such as retinal binding protein or microalbumin) can be used, which are stable in acidic urine. It should be noted that these biomarkers are not specific markers of cadmium- or lead-induced effects, because tubular renal dysfunction can also be caused by other exposures and diseases.

For both lead and cadmium, it is anticipated that for some age groups a health risk may exist, because dietary exposure already exceeds the health based guidance values (41, 42). Cadmium or lead intake from other sources are not included in these measurements, and for example for (young) adults, cadmium intake due to smoking cigarettes will probably result in a substantial exceedance of the TDI. With the aid of toxicokinetic models, the cadmium or lead concentration in blood or

urine of volunteers can be converted into their body burden and (assuming only oral exposure) into the external dose. These external doses can be compared to the TDI or BMDLs. The urinary levels of cadmium or lead can be compared to levels of endogenous biomarkers of kidney function (or tubular damage) and/or to the estimated glomerular filtration rate (eGFR) of these persons. The first comparison will probably show differences with the estimated dietary exposure due to additional routes of exposure. The second comparison may show a relation between urinary levels of cadmium or lead and reduced kidney function (or tubular damage) for certain population groups (e.g. heavy smokers at an advanced age). However, one should keep in mind that such a relationship needs to be carefully examined before a causal connection can be made. Moreover, the underlying mode of action(s) of cadmium and lead with respect to reduced kidney function should be examined in more detail.
In case biomonitoring would show that blood lead or urine cadmium levels are in a safe range, in contrast to what would be expected based on the dietary information combined with the health based guidance value, this would indicate that the applied margin of safety is sufficient. On the other hand, it is also possible that blood or urine levels are much higher than expected. This could be explained by exposure through different sources, but for example also when absorption from food or other sources is higher than assumed. In both situations, biomonitoring data will help in determining total exposure and the margin of safety with respect to the health based guidance value.
In addition, if biomonitoring would indicate that the body burden of a compound exceeds the health based guidance level, a second step could be to determine which routes and sources contribute to this systemic exposure and to which extent they contribute. Subsequently, research could be focused on measures that could be taken to decrease the exposure.

Furthermore, biomonitoring provides a good insight of interindividual variability in (internal) exposure and/or effect. However, it should be kept in mind that this variability is, most likely, caused by variability in (external) exposure and variability in toxicokinetics (differences in concentration-time profiles) and toxicodynamics (differences in dose-response profiles).

When sufficient information is available about the relationship between the body burden and the concentration of a substance in blood or urine, biomonitoring may in some cases be a relatively simple, fast, non-invasive (in the case of urine) and sometimes relatively inexpensive way to measure internal exposure. This body burden can then be used to estimate external exposure and/or effects.

Biomonitoring can be used in specific populations, in which exposure is suspected to be higher than usual. It was used for instance in the Billiton affaire in Arnhem in the 70s/80s, when it became clear that emission of toxic compounds and lead concentrations in groundwater in the area surrounding a local lead smelter was too high. The results showed that all employees of Billiton had excessive lead levels in their blood. Also children living around the lead smelter had remarkably high levels of lead in their blood. They were just below the threshold at that

time within the European Union. In the 90s the lead smelter of Billiton was closed, partly based on the results of the biomonitoring data (43, 44).
It has also been used as an additional tool to investigate whether people living in the (Dutch and Belgium) Kempen region have an increased risk of chronic kidney disease due to cadmium pollution caused by the nearby zinc smelter.

Of course, there are also some disadvantages of biomonitoring. For instance, a validated analytical method might not always be available for measuring a substance in a certain matrix, or the limit of quantification in the matrix of question might not be sufficiently low. Furthermore, endogenous biomarkers of particular effects may not be available. And, as already mentioned, most/all effect biomarkers are not substance specific. Only when a relation between for example blood concentrations of a substance and an effect is already established, the substance itself may be used to estimate if adverse effects are expected in a population.

6 Recommendations

In this chapter, some recommendations are given to study the biomonitoring of lead and cadmium in the near future.

The added value of the biomonitoring of lead and cadmium lies clearly in the area of the assessment of the realistic total (aggregated) exposure (in case of various routes of exposure) and of human health effects related to the realistic exposure to these chemicals (health impact assessment).
Depending on the extent and duration of the exceedance of the health based guidance value of lead or cadmium the chance that an adverse human health effect can be measured in practice will increase.
For lead a distinction between health effects for children and adults can be made. For children the critical effect is neurodevelopmental toxicity which can be reflected in young children in decreased cognitive functions, e.g. decreased IQ. Critical effects observed in adults are cardiovascular effects (systolic blood pressure) and decreased kidney function (e.g. decreased glomerular filtration). The latter effect can (theoretically) be observed at a lower body burden than needed for an increase of blood pressure and there are several validated methods to examine the extent of kidney malfunctioning. This can be done be measuring endogenous biological markers (proteins and/or enzymes) in blood and urine.
Also cadmium has a negative effect on kidney functioning and due to its accumulation in the kidney it is anticipated to exert a negative effect on kidneys in the elderly (above 60 years of age). Due to the chronic dietary exposure of cadmium this is a realistic concern, especially if dietary exposure is accompanied by exposure to cadmium through (long-lasting) smoking of cigarettes.

Summarised, it seems worthwhile to study biomonitoring of cadmium and lead for several reasons. First of all, cadmium and lead are well-established candidates for human biomonitoring and have a common critical effect on kidney functioning. Secondly, they offer the possibility to evaluate exposure and risk assessments of these compounds based on the determination of external doses. Thirdly, it is also possible to study human health effects (like kidney malfunctioning) in case health based guidance values are sufficiently exceeded. Especially when multiple route exposure can be assumed and health based guidance values are already exceeded through one route, e.g. through dietary exposure, it is expected that health effects can be measured in practice.

As mentioned above, kidney malfunctioning is a critical human health effect related to a (substantial) chronic exposure of cadmium and lead. This health effect can be studied in a sufficiently large population using a stepwise approach. The first step is to perform an analysis of strengths, weaknesses, costs and benefits of the available methods for measuring (sensitive) biological markers typical for different degrees of kidney disorder. Secondly, to select a national cohort study that has investigated (and possibly continuous to study) an appropriate population (of sufficient size, with a sufficient number of urine and blood

samples, etc.) including elderly with a sufficient percentage of smokers (people at risk). Thirdly, to analyse these samples for one or more biological markers and to try to identify groups of volunteers with different degrees of (supposedly) kidney disorder. Fourthly, to analyse samples of one or more of these selected groups for the presence of cadmium and/or lead. In case smokers can be distinguished from non-smokers it seems appropriate to start to analyse samples for cadmium, if the costs of analysis of both metals are limiting. Fifthly, to calculate body burdens of those volunteers for whom it has been shown that they have been exposed to lead and/or cadmium.

If body burdens are lower or higher than expected, these data may help in evaluating the margin of safety used in risk assessment. Particularly in the case of lead, the determination of the body burden of lead may help to confirm recent dietary exposures to lead, in case food is the main route of exposure. If body burdens of *e.g.* cadmium are higher than expected, it could be interesting to determine which routes and sources contribute to this systemic exposure and to which extent they contribute. Subsequently, research could be focused on measures that could be taken to decrease the exposure (of certain population groups).

This year an inventory will be published of the main characteristics of Dutch cohort studies (Tiesjema, te Biesebeek and Mengelers, 2017). This includes (amongst others) study design, number and life-style characteristics of participants, sample collection and storage and analysis of (basic) clinical-chemical parameters, etc. This report can be used to select a suitable cohort study (step two in the above-mentioned stepwise approach).

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Annex I: Chronic kidney disease and determination of renal function

For both lead and cadmium, the occurrence of chronic kidney disease is an important critical effect. Chronic kidney disease (CKD) is an irreversible, progressive reduction in renal function. Most patients are asymptomatic until the disease has significantly progressed. It is therefore essential to detect the condition in an early stage. The level of glomerular filtration rate (GFR), a measure for the amount of plasma which is being filtered in a certain time period, is widely accepted as the best indicator of overall kidney function. A decreased GFR and / or protein in the urine are signs of chronic kidney damage. Even mild renal damage already gives an increased risk for cardiovascular disease and mortality. The degree of kidney dysfunction, as assessed by the estimation of the glomerular filtration rate (GFR), is essential for the diagnosis, classification, and staging of CKD

The gold standard for determining kidney function is measuring the clearance of a substance that is removed unhindered by glomerular filtration and is not reabsorbed or secreted into the renal tubule. The clearance of such a substance is by definition equal to the GFR. Examples of substances that meet these requirements are foreign substances such as inulin and iothalamate. GFR measurements with these substances, however, are invasive, expensive and time-consuming and stressful for the patient. Therefore, in daily practice, GFR is often based on the serum creatinine. Creatinine is a muscle breakdown product mainly removed from the blood by glomerular filtration and excreted in the urine. However, small amount is actively secreted by tubular secretion, and therefore serum creatinine approximates GFR. As kidney function deteriorates, the amount of creatinine in the serum rises. It should be noted that the creatinine concentration in the serum is not only dependent on the renal function, but also on the amount of muscle tissue and muscle activity and is therefore dependent on gender, age, race, and body composition.

Due to these reasons, the serum creatinine concentration is not sufficiently precise to predict kidney function. In practice, the GFR is therefore determined based on the serum creatinine concentration by using the 4-point MDRD formula. The result reflects the estimated glomerular filtration rate (eGFR).

4-point-MDRD formula (expressed in ml / min / 1.73 m^2):
186 x (serum creatinine (in mmol / l) x 0.0113) -1.154 x (age (in years)) - 0.203 (1.212 x if black) (x 0,742 if female)

When using this method the following should be taken into account:

- For people with low body weight (<60 kg) or muscular atrophy, the MDRD formula overestimates the GFR.
- With increased muscle mass (e.g. muscular athletes and bodybuilders) the MDRD formula gives an underestimation of the GFR.

- The MDRD formula is less reliable at clearances above 60 ml / min / 1,73² (such a clearance is therefore listed as> 60 ml / min / 1,73m²)
- In persons older than 65 years an eGFR <60 mL / min / 1.73m^2 may be normal for their age, without indicating underlying renal disease
- The kidney function may be underestimated because of high serum creatinine concentrations due to the use of certain drugs (such as cimetidine, trimetroprim and co-trimoxazole) and heavy physical activity or meat consumption above average.
- During pregnancy, the normal values are 30% lower due to increased filtration

In young healthy adults up to 30 years, the GFR or creatinine clearance can be up to about 120 ml / min / 1.73 m^2 amounts. After this age, the renal function reduces by approximately 10 ml / min / 1.73 m^2 per 10 years.
For the classification of the degree of renal impairment usually the guidelines of the European Medicines Agency (EMA) or those of The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) are used (see table 1).

Table 1. Stages of Chronic Kidney Disease

Stage	**Description**	**GFR according to EMA**	**GFR according to NKF KDOQI**
1	kidney damage with normal or elevated GFR	> 80 ml/min/1,73 m^{2*}	> 90 ml/min/1,73 m^2
2	Kidney damage with mildly decreased GFR	50-80 ml/min/1,73 m^2	60-90 ml/min/1,73 m^2
3	Moderately decreased GFR	30-50 ml/min/1,73 m^2	30-60 ml/min/1,73 m^2
4	Severely decreased GFR	10-30 ml/min/1,73 m^2	15-30 ml/min/1,73 m^2
5	Kidney failure (ESRD)	<10 ml/min/1,73 m^2	<15 ml/min/1,73 m^2

* A GFR > 80 ml/min/1,73m2 indicates a normal renal elimination capacity. Therefore, in this stage of kidney damage there is only little damage, which does not affect GFR yet.

However, since 2016, in the Netherlands, Saltro determines the eGFR based on a new and improved formula: the CKD-EPI formula. The CKD-EPI formula uses the same variables as the MDRD formula: serum creatinine concentration, gender (1.16 x if black), age and race. The CKD-EPI formula has been validated based on the same data set from the MDRD study.

The CKD-EPI equation, expressed as a single equation, is:

$GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black]

Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or

The formula is also validated for eGFR values between 60 and 90 ml / min / 1.73m² and for persons over 70 years. In addition, a small loss of kidney function (eGFR between 60 and 90 ml / min / 1.73m²) is more reliably detected using the CKD-EPI formula. Young people are more often classified in a higher GFR class using the CKD-EPI formula, whereas older people are more likely to be classified into a lower GFR class when the CKD-EPI formula is used. The eGFR on the basis of the CKD-EPI formula thus leads to fewer "unwarranted" referrals to the 2nd line and an improved medication policy guided by renal function.
For the time being also the eGFR calculation using the MDRD formula will be reported.

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