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SHORT COMMUNICATION

Age differences in biological monitoring of chemical exposure: a tentative description using a toxicokinetic model

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Abstract
Aim Specific factors responsible for interindividual variability should be identified and their contribution quantified to improve the usefulness of biological monitoring. Among others, age is an easily identifiable determinant, which could play an important impact on biological variability.
Materials and methods A compartmental toxicokinetic model developed in previous studies for a series of metallic and organic compounds was applied to the description of age differences. Young male physiological and metabolic parameters, based on Reference Man information, were taken from preceding studies and were modified to take into account age based on available information about age differences.
Results Numerical simulation using the kinetic model with the modified parameters indicates in some cases important differences due to age. The expected changes are mostly of the order of 10–20%, but differences up to 50% were observed in some cases.
Conclusion These differences appear to depend on the chemical and on the biological entity considered. Further work should be done to improve our estimates of these parameters, by considering for example uncertainty and variability in these parameters.

Keywords Age · Toxicokinetic · Modeling · Biological indicators

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Introduction

Biological monitoring is a method widely used by occupational physicians to estimate chemical exposure. However, it is more and more often recognized that a large variability is associated with biological monitoring, making interpretation less efficient than foreseen (Truchon et al. 2006).

Toxicokinetic (TK) behavior of chemicals in the body determines biological levels and thus biological indicator results. It is usually described as four processes: absorption, distribution, metabolism and elimination. Biological variability comes from changes in these four processes.

In a recent review, Truchon et al. (2004) indicate that the question of the influence of age on industrial chemical toxicokinetics has received little attention. They recommend that this aspect should be further studied, notably by TK modeling, to better understand its contribution to biological variability. A few authors have started to describe, using various modeling tools, the contribution of age to biological variability. Some authors have described differences between children and adults (Kreuzer et al. 1997; O'Flaherty 1998; Hattis et al. 2003) and others have also taken in account the elderly (Jeandel et al. 1992; Clewell et al. 2002, 2004). Hattis et al. (2003) drew on individual data for pharmacokinetic and anthropometric parameters to help define distributions that will be helpful for population distribution modeling of pharmacokinetic differences between children of various ages and adults. Clewell et al. (2004) presented an initial attempt to provide a predictive pharmacokinetic framework to evaluate the potential impact of age- and gender-specific differences on risk from chemical exposure. The validation of these chemical-specific model predictions has been made with only young adult data.

It is presently still difficult to understand quantitatively the variability due to age associated with biological

monitoring results. Although it is possible to establish a list of contributing factors, as shown in a framework for age differences by Geller and Zenick (2005), their relative importance is unknown for different chemicals of occupational interest. It is therefore presently unfeasible to use such information to interpret biological variability and make safer quantitative decisions when using biological monitoring of exposure.

In preceding studies, Truchon et al. (2003) have developed TK tools to describe the influence of specific factors on biological levels, such as body build, physical workload, metabolic and excretion functions (Pierrehumbert et al. 2002; Truchon et al. 2006) but not age. One of these tools, namely a simple TK model, was applied in the present study to better understand the influence of age on biological exposure indicators. The report in question represents a tentative quantitative estimation of the effect of age on biological levels of several industrial chemicals and their metabolites. It is then applied to specific biological monitoring reference values.

Methods

Compartmental toxicokinetic model

A compartmental TK model developed in previous studies (Pierrehumbert et al. 2002) was applied to the description of age differences. The TK model (see Fig. 1, taken from Pierrehumbert et al. 2002) includes physiological parameters defining volumes and flows to be able to mimic age changes. It was adapted for each chemical according to available data and TK information.

The route of absorption by inhalation is represented in the model. In fact most of BEIs are based on a direct correlation with the TLVs, which indicate the potential "inhalation" exposure of a worker. Skin exposure is not included in the models. The chemical is distributed between the central compartment and the peripheral one, or storage compartment. These compartments can be illustrated by different tissues, depending on the chemical. The distribution can be either flow or diffusion limited and includes the permeability and affinity of the tissue for the chemical. The metabolism can give one or more metabolites, and can occur by serial or parallel metabolism. Elimination is represented by excretion in expired air, feces and urine or by metabolism. Information on the peripheral compartment when it exits can be found in Table 2. The central compartment is then composed of the resting tissues. The model is completely described by Pierrehumbert et al. (2002). The TK model was implemented in the simulation software ITHINK ANALYST (version 7.02 for Windows, High Performance System Inc., Hanover, NH, USA).

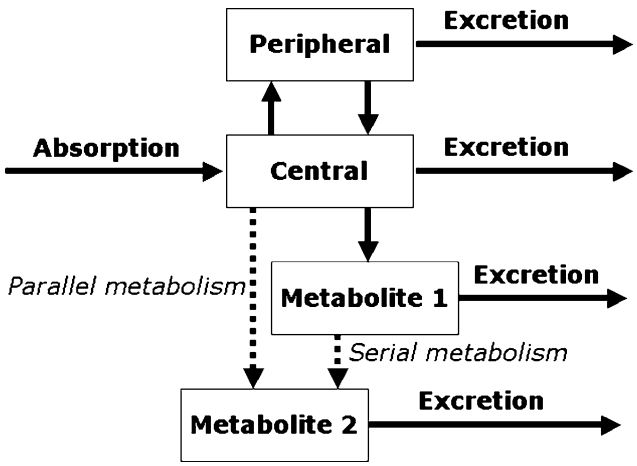

Fig. 1 Schematic diagram of the toxicokinetic model

Physiological and metabolic parameters

Young male physiological and metabolic parameters were taken from preceding studies and are based on Reference Man information (Tardif et al. 2002). These parameters, used to estimate specific data required for each chemical, were modified to take into account age based on known information about age differences. A 65-year-old man has been chosen, based on the legal retirement age in Switzerland, to model differences due to age. Furthermore, the present simulations do not take into account the apparition of various diseases with age and the increased use of medications. The main parameters required by the model structure are body weight, cardiac output, blood flows and volumes of the relevant tissues, renal clearances and metabolic constants. The detailed list of the parameters considered is presented in Table 1.

Changes in physiological and metabolic parameters

Clewell et al. (2004) developed separate sets of growth- and age-related equations. These relations give an increase in bodyweight of 5.5% from 25 to 65 years.

There is controversy about the effect of age on cardiac output. It has been described to decline with age (Birnbaum 1991). Clewell et al. (2004) have developed an age-related equation for cardiac output with data obtained from Åstrand (1983) and showed a difference of about 10% between the ages of 25 and 65 years. According to Tonner et al. (2003), cardiac output decreases in an almost linear fashion after the third decade of life, with a rate of about 1% per year in healthy individuals without prevalent cardiac disease. This would be a difference of 30% between the ages of 25 and 60 years. Fagiolino et al. (2006) indicate that cardiac output diminishes throughout life, changing 1%

Table 1 Parameters used in the TK models

Parameter		Unit[a]	Value[b] Age 25 years Rest 50 W	Variation (%)	Reference for the variation
BW	Body weight	kg	70	+5.50	Clewell et al. 2004
Qc	Cardiac output	$l/h/kg^{0.7}$	18.0 30.8	=	Ribera-Casado 1999; Ferrari et al. 2003
FV_{TBW}	Total body water (TBW)	l/kg	0.62	−15	McLean and Le Couteur 2004
FV_{fat}	Fat fraction of body weight	l/kg	0.19	+30	Kyle et al. 2001
FV_{liver}	Liver fraction of body weight	l/kg	0.026	−8	Chouker et al. 2004
FV_{kidney}	Kidney fraction of body weight	l/kg	0.004	−20	Epstein 1996; Silva 2005
BF_{fat}	Fat fraction of cardiac output	-	0.05 0.06	+30	Clewell et al. 2004
BF_{liver}	Liver fraction of cardiac output	-	0.26 0.16	−20	Zoli et al. 1999
BF_{kidney}	Kidney fraction of cardiac output	-	0.11 0.20	−25	Silva 2005
k_{ur}	Urinary excretion rate	$l/h/kg^{0.82}$	1.848	−30	Epstein 1996; Clewell et al. 2004
k_{cr}	Creatinine excretion rate	$\mu mol/h/kg^{0.9}$	12.06	−30	Epstein 1996; Clewell et al. 2004
RC	Renal clearance	$l/h/kg^{-0.3}$	–[c]	−30	Epstein 1996; Clewell et al. 2004
KM	Michaelis–Menten constant	µmol/l	–[c]	−8	Clewell et al. 2004
VM	Michaelis–Menten maximal rate	$\mu mol/h/kg^{0.75}$	–[c]	−8	Clewell et al. 2004

Age-related changes in physiological and metabolic parameters (age 65 years compared to age 25 years)

[a] The reference values are adjusted to the body surface using a formula where body weight is related to the body surface when raised at a given power

[b] Truchon et al. 2003

[c] Values are chemical-dependent

every year after the age of 25 years. On the other hand, Rodeheffer et al. (1984) demonstrate that there is no significant decline in cardiac output at rest or during exercise in healthy adults between the ages of 25 and 79 years. However, aging does alter the mechanism by which cardiac output is maintained during exercise. Ribera-Casado (1999) insists on the fact that in healthy elderly people, cardiac output remains practically unchanged. Ferrari et al. (2003), in a review about age and cardiovascular system, show that cardiac output is preserved with age in the resting heart. Based on these last references, cardiac output was considered here to remain unchanged with age for modeling purposes.

Concerning body composition, there is a progressive reduction in total body water and lean body mass, resulting in a relative increase in body fat with age (Mangoni and Jackson 2003). According to the ICRP (1975), the body fat fraction of weight is about 11% for a 20-year-old man and about 30% for a 70-year-old man. Several authors (Kyle et al. 2001; Turnheim 2003; McLean and Le Couteur 2004) mention that body fat increases by 20–40% and body water decreases by 10–15% in old age. For the TK models, body fat was considered to increase by 30% with age.

Clewell et al. (2004) analyzed data on brain and liver weights as fractions of body weight for a Japanese population. A calculation shows that the variation of liver volume between the ages of 25 and 65 years is about 6%. Le Couteur and McLean (1998) show that in general the reduction of liver size with age is noted to be of the order of 25–35%. After the report of the Task Group on Reference Man, liver weight decreases particularly after an age of 70 years (Snyder et al. 1975). Chouker et al. (2004) have developed formulas for the estimation of liver size upon data obtained on liver weight from 728 legal autopsies analyzed with respect to gender, age, body height, body weight, body mass index and body surface area. From these data, the decrease in liver size is about 8% between the ages of 25 and 65 years. Finally, on basis of the formulas developed by Chouker et al., a decrease of 8% has been retained for the TK model simulations.

Several authors describe the decrease of the kidney weight with age (Löf and Johanson 1998; Mühlberg and Platt 1999; McLean and Le Couteur 2004; Geller and Zenick 2005). The aging kidney shows a decrease in weight of about 20–30%, especially in the 70s and 80s (Silva 2005). Epstein (1996) mentions a decline in male kidney weight of 19%. For the TK models, a variation of 20% has been fixed.

Renal blood flow decreases after the fourth decade by about 10% each decade (Silva 2005) and this is not related to cardiac output. A variation of 25% was thus included in the TK models.

Age-related declines in hepatic blood flow ranging between <0.5 and 1.5% per year have been reported (Schmucker 2001). This would produce a greater than 40% decline between 25 and 90 years of age. According to

Anantharaju et al. (2002), when comparing subjects under 40 years to those over 65 years, there is a decrease of 35% in hepatic blood flow. Zoli et al. (1999) found a decrease of about 20% between subjects under 45 years and subjects between 61 and 75 years. Based on this information, a 20% reduction in hepatic blood flow was chosen for the TK models.

Clewell et al. (2004) calculate the age-specific metabolism rates by using the adult metabolism rate, the adult liver volume, the age-specific liver volume and the appropriate linearly interpolated fractional activity (gives enzyme activity as a fraction of the adult level). Different enzyme systems have been taken in account: CYP2E1, CYP1A2, CYP2C, ADH. As these fractional activities do not change between the young adult and the old adult, the changes of the metabolism rates will depend on the liver volume. For our TK models, we decided to use the same variation as for the liver volume, which is about 8%.

The parameter, which often determines renal function, is the glomerular filtration rate. Clewell et al. (2004) describe the age-related differences for urinary clearance parameters by a set of equations based on data on glomerular filtration rates. The variation is about 25% between a person of 25 years and one of 65 years. According to Epstein (1996) and Mühlberg and Platt (1999), those variations for the same ages can be about 30%, after a widely used formula developed by Cockcroft and Gault (1976) for estimating the creatinine clearance. Berg (2006) shows similar differences by using other methods (clearances of inulin and *para*-aminohippurate) for evaluating the glomerular filtration rate.

The skeleton bone tissues also show some decrease with age. The loss of bone has been estimated to be about 5–10% per decade, beginning at about 30 years of age (Snyder et al. 1975). A value has been fixed at 20% for the simulation of a young and an old individual. No value has been estimated for the richly perfused tissues fraction of bodyweight because of a lack of information.

Table 1 summarizes physiological and metabolic data used in the model in terms of changes between 25 and 65 years. All the values of the parameters that are chemical-dependent can be found in detail in Truchon et al. (2003).

Exposure scenarios

Repeated occupational exposures were simulated at the current threshold limit values (TLVs) (ACGIH® 2007): 8 h/day, 5 days/week until steady state was reached in the tissues. For the compounds having long half-lives, steady state was also reached, by adding for example an initial dose in the central compartment or by simulating the model over long exposure times. Physical workload was set at 50 W during 12 h (including the 8 h of exposure) and at 0 W the remaining of the day.

Results

Modeling age differences in biological levels

The TK model was applied to 14 chemicals, representing 21 specific biological entities. These chemicals are examples among the list of BEIs (Truchon et al. 2003). For each chemical, important physiological and metabolic parameters were identified and included in the model structure (Pierrehumbert et al. 2002). Results obtained while simulating the influence of age are summarized in Table 2 for the ages of 25 and 65 years.

These preliminary simulations indicate in some cases considerable differences due to age. Moreover, these differences appear to depend on the chemical and the biological entity considered. For some of them age does not seem to affect biological level; for others, TK calculations tend to show that age is an important determinant.

Changes are of the order of 10–30% for almost half the chemicals simulated by the TK model. About a quarter of the substances shows differences less than 10% and for the resting quarter variations are over 30%, with two examples up to more than 50%.

Application to biological monitoring data

Predictions presented in Table 2 can be applied to biological monitoring of exposure. Biological reference values represent biological levels that would be observed in fluids collected in healthy workers repeatedly exposed at a given reference air concentration. It can thus be expected that, due to age, different values would be observed. Table 3 presents levels that would be observed in 65-year-old workers, taking young workers as reference. This information could be used to improve our interpretation of biological monitoring results, unless better information is available.

Discussion

The TK model used here is relatively simple and do not represent each chemical's specific detail. More elaborated techniques, such as PBPK models, could give a better view of the effect of age. However, it would be more difficult to develop a general model for a category of chemicals describing the differences due to age.

The present results indicate that the influence of age is chemical-specific. Some chemicals seem to be hardly affected, while others show large differences. The same is indeed true when considering biological indicators of exposure.

For chemicals in blood, differences can be important due for example to the presence of a peripheral compartment in

Table 2 Tentative predictions of age-related changes in biological levels of some occupational chemicals and their metabolites (age 65 compared to age 25)

Biological indicator	Relative change (%) in $C_{\text{central comp.,blood}}$ Age 65 years versus age 25 years	Peripheral compartment	Relative change (%) in $C_{\text{peripheral comp.}}$ Age 65 years versus age 25 years	Relative change (%) in $C_{\text{metabolite comp.,blood}}$ Age 65 years versus age 25 years	Relative change (%) in $C_{\text{excretion,urine}}$ Age 65 years versus age 25 years
Arsenic	1.0				−14.5
Methylarsonic acid				11.3	−24.0
Methylarsinic acid				63.7	53.0
Cadmium	32.4	Kidneys	17.9		10.5
Chromium (VI)	21.9	rpt	20.4		14.1
Cobalt	7.8	rpt	6.2		−11.6
2-Ethoxyethanol	6.2				
2-Ethoxyacetic acid				38.3	34.8
Ethylbenzene	0.3	Fat	1.8		
Mandelic acid					10.3
Fluorides	31.5	Skeleton	35.9		22.9
Lead	25.8	Skeleton	18.9		
Manganese	27.2	Liver	48.2		7.0
Mercury	27.9	Kidneys	47.5		16.7
Methyl isobutyl ketone	19.8	Fat	17.7		44.0
Pentachlorophenol	33.5				7.3
Conjugated pentachlorophenol					10.7
Phenol	28.7				20.4
Toluene	3.2	Fat	5.1		
Hippuric acid				29.8	13.6
o-Cresol					10.9

rpt richly perfused tissues

the TK model. Changes due to age like the lean body fraction, the kidney fraction or the liver fraction of bodyweight could explain an increase in the blood concentration of a substance. When the peripheral compartment is represented by the volume of body fat, differences are not so important. Changes in body mass, or more specifically in total body water and body fat, will have an influence on the distribution volumes of a chemical. The consequence can be an increased concentration of hydrophilic substances and a prolonged half-life for a lipophilic substance. Products with a fast metabolism seem to have a little impact with age on the blood concentration. In the case of the concentration in the peripheral compartment, it seems to increase with age when the target organ is represented by the liver or the kidneys. When looking at the differences due to age for the metabolic and excretion compartment, it is evident that for several chemicals the elimination parameters like the excretion rate have a significant impact on the concentrations. In very few cases, there is a decrease in the urinary concentration of the substance when the aged person is compared to the younger one, which could be explained by the interindividual variablity. Thus, it seems difficult to set up simple rules for a category of chemicals, each chemical being a specific case, which has to be investigated on its own. Parameters like metabolism, storage, long half-lives, hydrophilic or lipophilic property of a chemical are often chemical-specific. It is not evident to do some classification like organic and inorganic products, or lipophilic and hydrophilic substances because in both cases important and less important differences exist.

In this context, TK models seem to be appropriate tools. It is therefore essential to study and describe not only some specific chemicals but also the mechanism underlying those changes to be able to forecast changes for new chemicals.

When compared to global biological variability expected in workers (Lin et al. 2005; Truchon et al. 2006), which is about 30%, the tentative predictions made here indicate that age could be in some cases an important determinant of variability. The variability extent index estimated by Truchon et al. (2006), which had not taken into account variability due to age, shows that, in some cases, the simulated value of a 65-year-old worker can be out of the estimated

Table 3 Predicted biological reference values in 65-year-old workers

Chemical/biological indicator	Sampling time[a]	Corresponding exposure level	BEI[b]	VEI[c]	Simulated value Age 25 years	Simulated value Age 65 years	Expected change (%) Age 65 years versus age 25 years
Arsenic		0.01 mg/m^3					
Inorganic arsenic and its metabolites in urine	EW		35 µg As/l	14.2–66.9	63.7	84.2	32
Cadmium		0.01 mg/m^3					
Cadmium in urine	NC		5 µg/g creatinine	1.6–14.9	4.7	5.6	19
Cadmium in blood	NC		5 µg/l	3.8–6.5	1.2	1.7	42
Chromium (VI)		0.05 mg/m^3					
Chromium in urine	ESW		25 µg/l	15.4–72.3	43.9	51.9	18
Cobalt		0.02 mg/m^3					
Cobalt in urine	ESW		15 µg/l	4.7–17.9	10.4	9.8	−6
Cobalt in blood	ESW		1 µg/l	0.59–1.18	0.85	0.92	8
2-Ethoxyethanol		5 ppm					
2-Ethoxyacetic acid in urine	ESW		100 mg/g creatinine	41.5–244.1	68.7	94.1	37
Ethylbenzene		100 ppm					
Mandelic acid in urine	ESW		0.7 g/g creatinine	0.6–3.8	1.6	1.8	13
Fluorides		2.5 mg/m^3					
Fluorides in urine	PS		3 mg/g creatinine	1.2–7.9	3.4	3.5	3
Fluorides in urine	ES		10 mg/g creatinine	4.5–22.4	9.4	10.6	13
Lead		0.05 mg/m^3					
Lead in blood	NC		300 µg/l	161.2–561.6	188.5	217.6	15
Mercury (inorganic)		0.025 mg/m^3					
Mercury in urine	PS		35 µg/g creatinine	10.6–113.6	30.8	35.1	14
Mercury in blood	ESW		15 µg/l	9.2–25.1	13.6	16.7	23
Methylisobutylketone		50 ppm					
Methylisobutylketone in urine	ES		2 mg/l	0.8–5	4.1	6.1	49
Pentachlorophenol		0.5 mg/m^3					
Conjugated pentachlorophenol in urine	PSW		2 mg/g creatinine	0.9–4.2	1.8	2.1	17
Pentachlorophenol in blood	ES		5 mg/l	2.7–10.1	3.7	4.7	27
Phenol		5 ppm					
Phenol in urine	ES		250 mg/g creatinine	97.4–511.4	327.9	402.1	23
Toluene		20 ppm					
o-Cresol in urine	ES		0.5 mg/l	0.16–1.53	0.98	1.09	11

[a] Time of sampling: *ES* end of shift, *EW* end of workweek, *ESW* end of shift at end of workweek, *NC* not critical, *PS* prior to shift, *PSW* prior to last shift of the workweek

[b] *BEI* biological exposure indices (ACGIH® 2007)

[c] *VEI* variability extent index with the 95% limit values (Truchon et al. 2006)

interval of values. It is also interesting to notice that in several cases the simulated values exceed the biological exposure indices. In very few cases, there is a decrease in the urinary concentration of the substance when the aged person is compared to the younger one. Predictions of age differences in biological indicators were made based on typical values for specific physiological and metabolic parameters. Further work should be done to improve our estimates of these parameters and in consequence their influence. Notably, uncertainty and variability in these parameters could be considered, using for example Monte–Carlo simulations. Further studies, like human volunteer exposure, need to be done to reach a better quantitative description of age differences in biological monitoring results.

Furthermore, the present predictions do not take into account the apparition of various diseases with age and the increase use of medications. These aspects would probably enhance differences. The present predictions should therefore be considered as minima to be expected.

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