Environmental Health Perspectives
Vol. 28, pp. 211–217, 1979

Metabolic Model for Cadmium in Man

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A metabolic model for cadmium has been formulated in terms of a flow scheme for cadmium among eight body compartments. The mathematical description of the flow of cadmium between compartments consists of a number of differential equations, and the accumulation of cadmium may thus be calculated. Coefficients for the flow of cadmium were estimated from empirical data both from animals and man. The modelling serves two main purposes: it provides a means of using present knowledge about metabolism in order to calculate expected accumulation in critical organs and other tissues and body fluids at certain intake levels and it makes it possible to define deficiencies in our present knowledge about metabolism. Data recently collected, partly as a result of considerations related to the model, have confirmed the assumptions of a very long biological half-time in other tissues and the small excretion of cadmium via bile.

Introduction

Based on the behavior of a chemical compound after a single administration, compartment models may be formulated describing the metabolism of the compound in terms of distribution volumes and clearances from plasma by exchange and excretion. Such metabolic models have been formulated for a number of chemical compounds used as drugs and has recently been used also for some metals (*1*). Although it is theoretically possible to use a similar approach when formulating a model for cadmium, several characteristics of the metabolism of cadmium makes such an approach less applicable. The complete lack of data concerning plasma values of cadmium in human beings also makes it impossible for the present studies.

In formulating the present model, a completely different approach was used. Based on a review of the literature concerning cadmium metabolism in animals and man as well as our own experience in this field, as much as possible of this information both in qualitative and quantitative terms was fed into the modelling procedure. The access to computer systems is presently widespread and the work involved in actual computation processes is therefore eliminated. In view of this we have not attempted to limit the number of compartments in our model at the cost of excluding interesting body compartments. The model to be presented thus includes as many as eight compartments.

A one-compartment model for calculation of cadmium accumulation in the kidney cortex has previously been used by us (*2, 3*). It has however, been pointed out that such a model is very approximate and may generate erroneous values for some exposure situations. Also, it does not describe the relationships between cadmium concentrations in different organs and body fluids.

The present paper presents a discussion of the procedure chosen in formulating the eight-compartment model. A comparison of the model with newly obtained data on cadmium metabolism is also presented. A more detailed description of the model has been given elsewhere (*4*).

Formulation of the Model

The flow scheme describing the model is shown in Figures 1 and 2. *A* is the amount of airborne cadmium that is inhaled and *G* is the amount of cadmium ingested. The part of the model depicted in Figure 1 is a description of known conditions with regard to the deposition and absorption of particulate matter as has been known for many years and described by the Task Group on Lung Dynamics 1966 (*5*) and Task Group on Metal Accumulation 1973 (*6*). Cadmium particles deposited on the mucociliary escalator thus will be transferred to the

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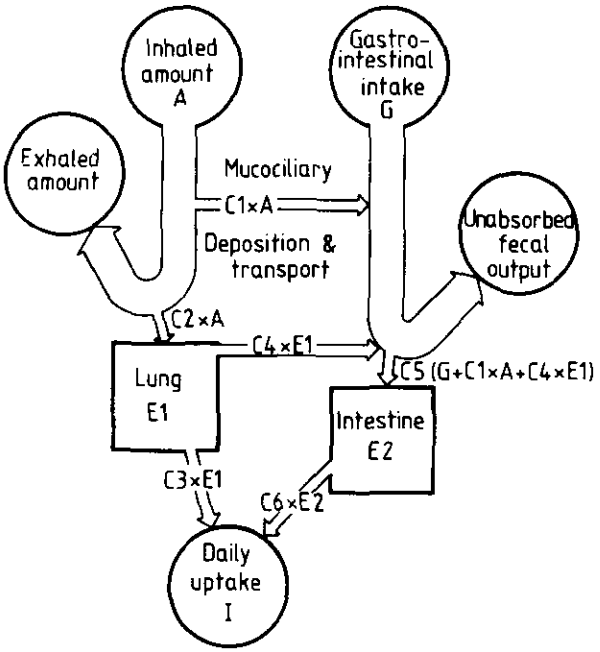

FIGURE 1. First part of flow diagram of metabolic model, describing uptake through lung (5) and gastrointestinal tract (6).

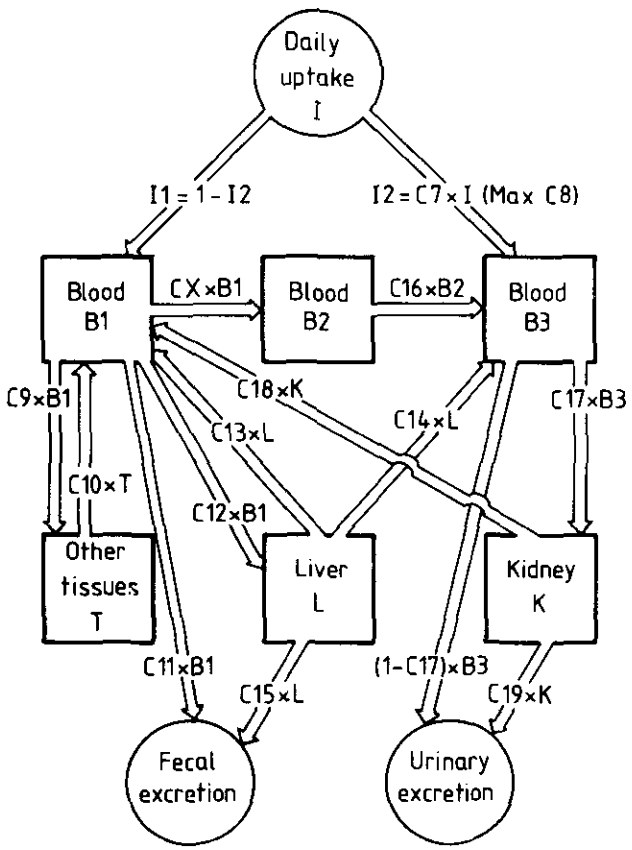

FIGURE 2. Flow diagram of metabolic model of cadmium after uptake from lung or gastrointestinal tract has taken place (according to Fig. 1.)

gastrointestinal tract ($C_1 \times A$) and cadmium particles deposited alveolarly ($E_1 = C_2 \times A$) will either be transferred to the mucociliary escalator and the gastrointestinal tract ($C_4 \times E_1$) or to the systemic circulation ($C_3 \times E_1$).

In the same manner, the gastrointestinal uptake is modelled by assuming that a certain fraction of the amount of cadmium that is present in the gastrointestinal tract will be taken up into the intestinal mucosa (E_2). Of the amount present there a certain fraction will be taken up into the systemic circulation daily ($C_6 \times E_2$).

The amount transferred daily to the systemic circulation (daily uptake I) will be distributed among three blood compartments (Fig. 2). It seems that at this point the model becomes rather complicated, including as many as three different compartments in blood. However, this was necessary in order to get the model to represent whole blood values which are frequently used in evaluation of cadmium exposure. Plasma values are generally not used for cadmium because they are so low that it is extremely difficult to determine these values from an analytical chemical point of view. The introduction of the blood compartment 2 (blood 2), represents the accumulation of cadmium in erythrocytes, and this cadmium will be unavailable for distribution in the same manner as cadmium bound to various plasma proteins. Of the daily uptake one part was assumed to be bound directly to metallothionein (blood compartment 3). However, there is reason to believe that the amount of cadmium that could be bound to metallothionein directly in plasma is limited, since the amount of circulating metallothionein is extremely small. On the other hand, there are a number of other possible binding sites in plasma, among them the SH groups on albumin (B_1). Since such binding sites are abundant, it is assumed that cadmium not bound to metallothionein in plasma will instead be bound to these other binding sites ($I_1 = 1 - I_2$). The amount of cadmium reaching blood compartment 1 (B_1), will transfer its cadmium content further to the various tissues in the body and a certain small proportion of the cadmium in these compartments will also be transferred back to blood 1. However, since the binding of cadmium in the various tissues is so much stronger than the one represented by the ligands in blood 1, the transfer from blood 1 to the tissues will be much more efficient than the transfer back from them. This means that C_9 is much larger than C_{10}, and C_{12} is much larger than C_{13}. A certain part of the cadmium in blood will be transferred into the feces through the intestinal mucosa ($C_{11} \times B_1$). A certain part of the liver cadmium will be released in the form of metallothionein to blood 3 ($C_{14} \times L$) and a very

Table 1. Assumed and modelled values of coefficients.

Coefficient	Initially assumed ranges[a]	Values fitting empirical data (corresponding biological half-time)	
C_1	0.1–0.2 (cigarette smoke)	0.1	
	0.4–0.9 (factory dust)	0.7	
C_2	0.4–0.6 (cigarette smoke)	0.4	
	0.1–0.3 (factory dust)	0.13	
C_3	0.01–1, day^{-1}	0.05	
C_4	0.1 × C_3 = 0.001–0.1, day^{-1}	0.005	
C_5	0.03–0.1	0.048	
C_6	0.05, day^{-1}	0.05	
C_7	0.2–0.4	0.25	
C_8	0.5–5, μg	1	
C_9	0.4–0.8	0.44	
C_{10}	0.00004–0.0002, day^{-1}	0.00014	(13 yr)
C_{11}	0.05–0.5	0.27	
C_{12}	0.1–0.4	0.25	
C_{13}	0–0.0001, day^{-1}	0.00003	
C_{14}	0.0001–0.0003, day^{-1}	0.00016	(7.5 yr)
C_{15}	0–0.0001, day^{-1}	0.00005	
C_{16}	0.004–0.015, day^{-1}	0.012	(54 day)
C_{17}[b]	0.8–0.98	0.95	
C_{18}	0–0.0001, day^{-1}	0.00001	
C_{19}[c]	0.00002–0.0002, day^{-1}	0.00014	(12 yr)
C_X	0.01–0.05	0.04	
C_{20}	0.05–0.5	0.1	
C_{21}	0–0.000002, day^{-1}	0.0000011	

[a] If no unit is given, it means that the coefficient is a unitless proportion.
[b] C_{17} decreases from age 30 to age 80 by 33%.
[c] C_{19} increases from age 30 with C_{21} each year.

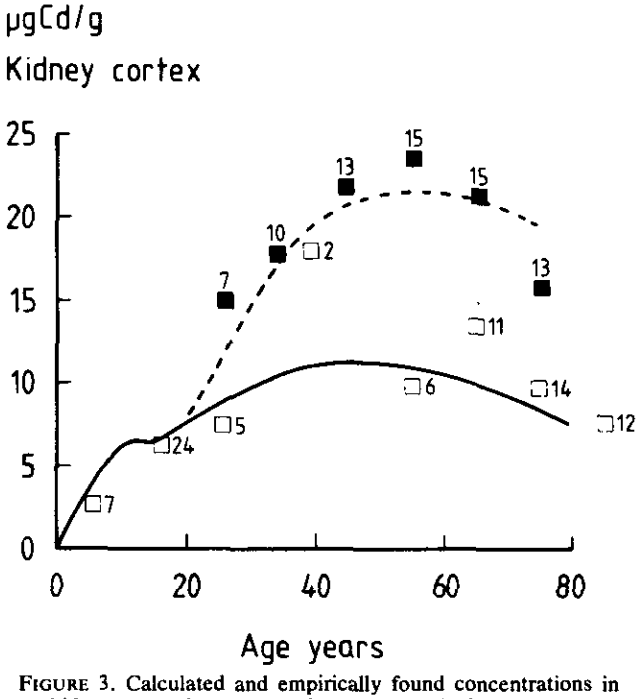

FIGURE 3. Calculated and empirically found concentrations in kidney cortex by age (Sweden); (——) calculated, nonsmokers; (--) calculated smokers; (□) observed, nonsmokers; (■) observed, smokers. Figures show number of observations.

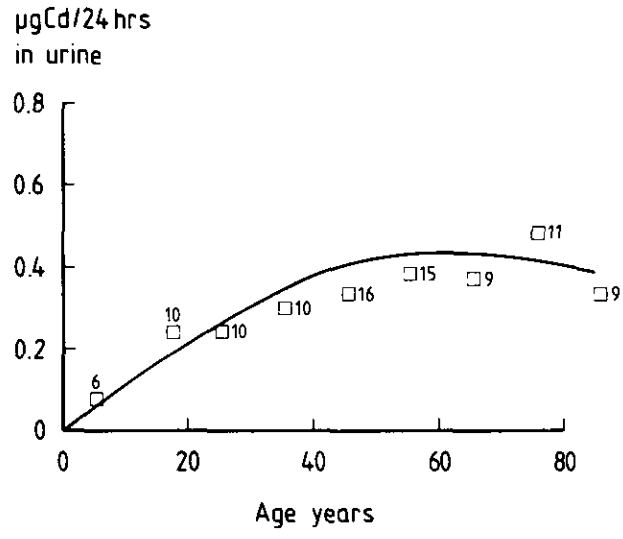

FIGURE 4. Calculated and empirical concentration of cadmium in urine by age (Sweden): (——) calculated excretion; (□) observed.

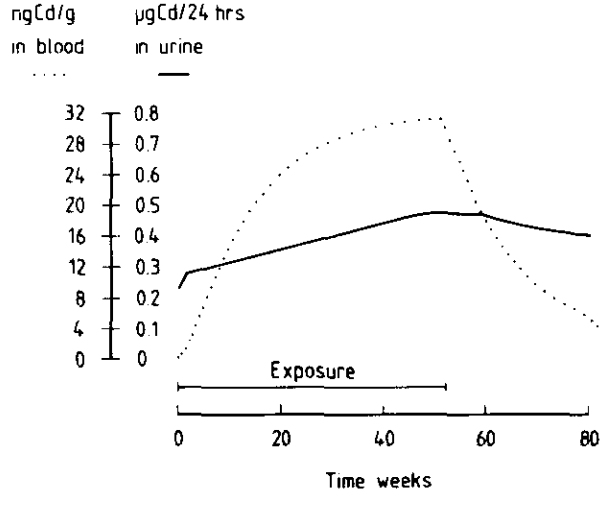

FIGURE 5. Calculated cadmium concentrations in blood and urine for newly employed workers in a battery factory (age 30) exposed for one year. Values at zero time represent pre-exposure values.

small proportion will be excreted in the bile (C_{15} × L). The kidney derives its cadmium content in this model exclusively from the metallothionein fraction in plasma. This is based on data from animal experiments demonstrating a selective uptake of metallothionein-bound cadmium in kidneys (*7*). There is, however, reason to believe that some small initial part of kidney cadmium may be arriving

there directly from B_1, but this will in all ordinary circumstances be a very minor proportion in relation to the amount that is transferred there from metallothionein (a possible exception would be acute exposures). A very minor part of blood 3 (5%) is transferred to the urine. Since there is reason to believe that the renal tubular reabsorptive capacity is diminished with age, C_{17} was made partly age dependent. The values for the various coefficients C_1 through C_{21} were initially set at certain intervals which could be obtained from data in the literature and general considerations regarding the various pathways. Values within these intervals were chosen when comparing the results of calculations by the model with actual empirical data collected parallel to the development of this model. These values are shown in Table 1.

The biological half-time of cadmium in "other tissues" (T) was unknown, but it was known (*3*) that the half-time for the whole body ranged from 10 to 30 years and that approximately half of the body cadmium would be in other tissues in adults. A relatively long biological half-time was therefore assumed for this compartment.

The flow of cadmium between the compartments in the model was described by a series of differential equations. The accumulation curves of cadmium in each compartment was calculated with an iterative procedure (iteration steps = one time unit) without solving the equations (i.e., numerical solution). The equations are shown in Table 2. The volume of the various compartments were those of an average person according to Documenta Geigy 1970 (*4*). As in previous calculations, the concentration of cadmium in the kidney cortex was assumed to be 1.5 times that of the whole kidney. Daily intake of cadmium via food was assumed to be age-related in the same way as calorie intake (*3*, Fig. 4.32).

Determination of Coefficient Values and Testing of Model

The coefficient values that gave the best fit of calculated and observed values for cadmium concentration in various compartments were chosen on basis of trials with calculation of various alternatives. The alternatives which gave a reasonable fit to data from Swedish smokers, persons newly employed in work involving cadmium exposure, persons with long-term occupational exposure, and persons in the Japanese general population without occupational exposure at different levels of daily cadmium intake via food were used. The model was further tested in relation to data from Swedish smokers and Japanese populations with background exposure and with high exposure. The resulting coefficients are shown in Table 1.

Figure 3 shows a comparison between empirical data from Elinder et al. (*8, 9*) and calculated concentrations of cadmium in the kidney cortex of Swedes who have an average daily intake of 16 μg of cadmium via food as adults (*10*). The calculated values are derived by using the coefficients listed in Table 1 as "values fitting to empirical data" and the equations listed in Table 2. Intake from smoking (upper curve) was 3 μg/day from age 20, corresponding to smoking 20 cigarettes per day.

Figure 4 shows a comparison for urine values of a

Table 2. Mathematical equations[a].

	Equation
Lung, exogenous compartment:	$E_1(t+1) = E_1(t) + C_2 \times A(t) - E_1(t) \times (C_3 + C_4)$
Intestines, exogenous compartment	$E_2(t+1) = E_2(t) + C_5 \times [G(t) + C_1 \times A(t) + C_4 \times E_1(t)] - C_6 \times E_2(t)$
Daily absorbed amount of cadmium	$I(t+1) = C_3 \times E_1(t) + C_6 \times E_2(t)$
	$I_2(t+1) = C_7 \times I(t+1) \leq C_8$
	$I_1(t+1) = I(t+1) - I_2(t+1)$
Blood compartment 1	$B_1(t+1) = I_1(t+1) + C_{10} \times T(t) + C_{13} \times L(T) + C_{18} \times K(t)$
Blood compartment 2	$B_2(t+1) = B_2(t) - C_{16} \times B_2(t) + B_1(t) \times (1 - C_9 - C_{11} - C_{12})$
Blood compartment 3	$B_3(t+1) = I_2(t+1) + C_{14} \times L(t) + C_{16} \times B_2(t)$
Whole blood	$B_4(t+1) = B_2(t+1) + C_{20} \times [B_1(t+1) + B_3(t+1)]$
Liver	$L(t+1) = L(t) + C_{12} \times B_1(t) - L(t) \times (C_{13} + C_{14} + C_{15})$
Kidney	$C_{19}(t) = C_{19}$ if $t \leq 30$ years
	$C_{19}(t) = C_{19} + C_{21} \times n$, if $t > 30$ years
	$n = 1, 2, 3, \ldots\ldots\ldots$; n increased once/year,
	$K(t+1) = K(t) + C_{17}(t) \times B_3(t) - C_{18} \times K(t) - C_{19}(t) \times K(t)$
Other tissues, endogenous compartment	$T(t+1) = T(t) + C_9 \times B_1(t) - C_{10} \times T(t)$
Whole body	$W(t+1) = B_4(t+1) + L(t+1) + K(t+1) + T(t+1) + E_1(t+1) + E_2(t+1)$
Fecal excretion (excluding nonabsorbed cadmium from GI intake)	$F(t+1) = C_{11} \times B_1(t) + C_{15} \times L(t)$
Urinary excretion	$U(t+1) = B_3(t) \times [1 - C_{17}(t)] + K(t) \times C_{19}(t)$

[a] The initially assumed ranges for the coefficients C_1 to C_{21} are listed in Table 1.

Table 3. Calculated and empirical cadmium concentrations in various tissues for a Japanese resident of Tokyo at age 45 with a 40 μg daily cadmium intake via food and 2.7 μg via air.[a,c]

Tissue[b]	Cd concn	
	Observed	Calculated
Kidney cortex, μg/g	65	48
Liver, μg/g	3.4	3.2
Other tissues (muscles), μg/g	0.2	0.18
Blood, μg/g	4.5	3.4
Urine, μg/l.	1.1	1.3[d]

[a] Data compiled from Tsuchiya and Iwao (*11*), Tsuchiya, Seki and Sugita (*12*) and Harada, Taniguchi and Sato (*13*).

[b] Tissue weights 76% of average tissue weights for a Swede (except urine), 4.8% gastrointestinal absorption.

[c] Based on 75% smokers smoking on an average 24 cigarettes per day in the general population of Japan (Japan Monopoly Company, 76) (*14*). Smoking assumed to start at age 20.

[d] Cd in 24 hr period.

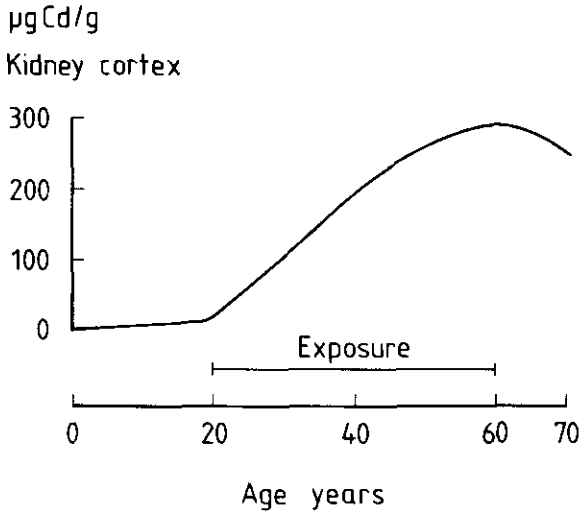

FIGURE 6. Calculated concentrations of cadmium in kidney cortex of workers in a battery factory exposed from age 20-60 to 50 μg Cd/m³ of industrial air.

Swedish population (*9*). In all these cases the calculated values fit well to those found empirically.

Values calculated with the model also compare favorably with data (*11–14*) from Japanese studies (Table 3).

It should be pointed out that data for blood unavailable at the time when the modelling was done, were very uncertain; at the present, data on blood cadmium on workers with defined exposure history are still not available to any large extent. It is therefore necessary to regard the modelling of blood values as tentative. A comparison of the relatively small increase in urine values and the substantial increase in blood values predicted by the model for a worker with one year exposure to cadmium is shown in Figure 5. These relationships are in agreement with empirical observations in newly exposed workers (*4, 15, 16*).

The renal accumulation of cadmium is of special interest, since effects on this organ are regarded as critical. In Figure 6 the renal cortical concentrations calculated by the model in the course of industrial exposure to 50 μg/m³ of Cd in air from age 20 to 60 are shown. It may be seen that it would take approximately 20 years of exposure to reach 200 μg/g in renal cortex.

The daily intake via food giving rise to 200 μg/g in renal cortex was also calculated based on an age-related cadmium intake similar to calorie intake (*3*). The present model predicted that a daily intake corresponding to 440 μg at age 50 would give 200 μg/g of cadmium in kidney cortex at age 45–50.

Discussion

A few things that emerged in the modelling procedure may deserve special comment. As mentioned before it was not possible without using three blood compartments to model blood concentrations in a reasonable way. Insufficient data are available at present to show whether the modelling for blood is accurate or not, but such data would be most interesting to get. In this context it may be mentioned that recent data by Elinder (*17*) on blood and liver concentrations in Swedes were shown to compare favorably with the model. The biliary excretion of cadmium was set at a very low value in the model. Some data in the literature pointed towards a high excretion of cadmium via bile in man (*18*), but this would not fit reasonably well in the modelling procedure. In view of this and the very low values obtained in animals, (*19*) a low excretion by this route was assumed. Recent data by Elinder (*17*) point towards a relatively low biliary excretion in man, giving some support to the assumptions in the present model of a low excretion of cadmium via this route. The data by Elinder (*17*) on cadmium concentrations in human bile showed an average concentration of about 2.5 μg/g wet weight. The corresponding average liver value (smokers + nonsmokers) was 6.9 μg/g dry weight, which corresponds to 1.8 μg/g wet weight. With a liver weight of 1.5 kg this would mean a total of 2.7 mg of cadmium in the liver compartment.

The excretion coefficient in the present model (C_{15} = 0.00005/day) would mean a total excretion via bile (2700 × 0.00005) of 0.135 μg/day. With a bile flow of 500 g this would mean a concentration of 0.27 ng/g. In view of the fact that the bile is concentrated several times in the gall bladder (and if cadmium is not reabsorbed in this process) the values found by Elinder for gall bladder bile may be

said to agree fairly well with values predicted by the model. However, the data on cadmium concentrations in bile from the choledochus (1-155 ng/g) do not agree with values calculated by the model.

Only by assuming a very long biological half-time of cadmium in other tissues, could the present model be fitted with reasonable accuracy to empirical data. At the time of the modelling, no information on the accumulation procedure of cadmium in "other tissues" was available in human beings, only some point observations of very scarce nature at certain age groups. It is thus interesting to see that recent data presented by Kjellström et al. (*16*) demonstrate a very long biological half-time as reflected in a continuous accumulation in muscle during the lifetime.

Recent data by Flanagan et al. (*20*) on the gastrointestinal absorption of cadmium in humans show a mean value of about 5%, which is in accord with the present model. Flanagan et al. observed, however, that the absorption in females was higher than in males and that the difference was due to low iron stores in females. Up to 20% of cadmium was absorbed in one case. These observations demonstrate the need to identify susceptible groups in the human population and to study the metabolism of cadmium in such groups. In order to use the model for calculation of exposures that would protect even such susceptible groups from adverse effects, values valid for such groups must be used in the modelling procedure.

When calculating intakes giving rise to a certain concentration in kidney cortex, the present model would be expected to generate similar values as the one-compartment model previously used by us (*3*) at exposures of several decades. For example, in the tables presented by Friberg et al. (*3*), the daily cadmium intake via food required to reach 200 μg/g in kidney cortex at age 50 was calculated to be between 352 and 616 μg (at biological half times in kidney of 19 and 9.5 years, respectively). Our present model arrived at 440 μg (biological half-time in kidney = 12 years). On the other hand, for shorter exposures like those of interest for industrial workers, a difference between the present eight compartment model and the previous one compartment model is to be expected. Even at an exposure time of 25 years there is an obvious difference between the models. Whereas the one-compartment model predicted a required concentration in industrial air of 11.1–15.8 $\mu g/m^3$ (9.5–19 years half-time and 25% absorption by inhalation), the present eight-compartment model arrives at approximately 40 $\mu g/m^3$ in order to reach 200 μg/g in renal cortex of a worker exposed to cadmium for 25 years (Fig. 6). Even if the values are corrected for the difference in assumed absorption (25% in the previous model and about 18% in the present model) there will still be a difference by a factor of 2 between the two models. At shorter exposure alternatives the difference will be larger.

Further research is needed in order to confirm some of the assumptions made in the present model, however it can be concluded already now, that calculation of, for example, renal concentrations based on the present model can serve a useful purpose. This has been shown in the evaluations in relation to empirically found dose-response relationship in the studies by Kjellström (*21*). The modelling procedure also points out the gap in knowledge concerning certain important aspects of cadmium metabolism. Data are presently being collected in order to fill out these gaps in our knowledge.

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