DEVELOPMENT AND EVALUATION OF A PHYSIOLOGICALLY-BASED KINETIC MODEL FOR THE TRANSFER OF LEAD IN LACTATING NIGERIAN WOMEN WITH HIGH AND LOW EXPOSURE TO LEAD

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ABSTRACT

This study aimed to develop a physiologically-based kinetic model for lead and to predict the kinetic behavior of lead in lactating mothers with the model under different scenarios. The model consisted of the following compartments: the lungs and the digestive tract through which lead enters the systemic circulation, the blood, the cortical bone, the trabecular bone, the soft tissues, the breastmilk and urine. Maple 13 was used to solve the generated model equations numerically (taking into account the mass balance principle). The model was used to simulate tissue lead concentrations in lactating mothers. Evaluation of the predicted concentrations was carried out using experimental data of 27 lactating mothers from Zamfara gold mines (high exposure) and 50 mothers from Ile-Ife (low exposure), both in Nigeria. The model was further used to study how various exposure scenarios such as intermittent exposure, massive medication, low medication, physiological changes (such as pregnancy) influence the levels of lead in key body compartments of female subjects. For massively chelated subjects, blood lead level dropped to 58 μg/dl from 274 μg/dl while milk lead level was reduced to 24 μg/dl from 81 μg/dl. For subjects with low medication, the milk lead level dropped to 154 μg/dl from 274 μg/dl while the milk lead level reduced to 58 μg/dl from 81 μg/dl. The result of the model developed showed that turnover of lead from bone to blood was more in lactation (63%) than in pregnancy (26%). With appropriate values for individual body height and body weight, the simulation results of the model developed in this study were in agreement with the blood experimental data in both Zamfara (χ^2=0.0056, r=0.557 at 0.01 significance level) and Ile-Ife (χ^2= 0.0086, r=0.7851 at 0.01 significance level).The physiologically based kinetic model developed was an effective approach in predicting tissue lead levels in adult female subjects and also intakes in their breastfed infants based on exposure lead data from mothers.

Keywords: PBK Model, Lead, Blood, Breastmilk, Lactating Mothers

INTRODUCTION

Of all the toxic trace elements, lead has attracted more attention from researchers lately in Nigeria. This is because lead has been found to be instrumental to the increase in mortality rate of the populace, especially women and children in recent years. This has been attributed to the extensive past use of leaded fuel in the country and unregulated mining in lead-rich areas. Of serious concern is the recent Zamfara lead poisoning where hundreds of children died of poisoning in some communities (notably Bukkuym and Anka) renowned for unregulated gold mining in Zamfara State (Ojo *et al.,* 2013). Although, the use of leaded fuel ceased in the country many years ago, its effect is still being felt. This is as a result of release of stored lead in the bones to the blood (endogenous exposure) since lead is known to have a half life of 20 to 30 years in the bones (Rabinowitz, 1976). However, skeletal lead poses no threat until the body undergoes physiological stress (such as in pregnancy and lactation) when it is released into the blood and subsequently excreted in the breastmilk. This puts women and children at greater risk of lead poisoning. Children are however the most vulnerable because they depend solely on breastmilk for their nutrition for at least the first six months of life and they have immature blood-brain barrier (Dorea, 2003).

Although several physiologically based kinetic models exist for lead (Rabinowitz *et al.,* 1976; Bert *et al.,* 1989; Leggette, 1993), no such model has been developed for assessing possible infant exposure to lead through breastmilk. This study was therefore designed to develop a physiologically based kinetic model for the

prediction of infant level of endogenous lead exposure through breastmilk following intakes by the mother.

A physiologically-based kinetic (PBK) model involves the development of mass balance differential equations to describe the Absorption, Distribution, Metabolism and Excretion (ADME) processes of elements as a function of their physiochemical (e.g. tissue, blood partition coefficient), biochemical (e.g. metabolic rate constant) and physiological characteristics (Devillers, 2009).

Rabinowitz *et al.* (1976) and Bert *et al.* (1989) developed physiologically-based kinetic models to estimate internal dose for lead in humans. In the Bert model, the bone was divided into two compartments (cortical bone and trabecular bone) unlike that of Rabinowitz in which the bones were lumped together, resulting in a simpler model with just three compartments (Blood, Bone and soft tissues). In this paper, a more complex model involving eight compartments (lungs, digestive tract, blood, cortical bone, trabecular bone, soft tissues, breastmilk and urine) is proposed that can describe the kinetic behavior of lead and permit the evaluation of infant exposure through breastmilk.

METHODOLOGY

Description of the Model

The body is considered to consist of eight compartments (as shown in Figure 1). The compartments are; blood, cortical bone, trabecular bone, soft tissues, breastmilk, urine, lungs and the digestive tract. The main routes of exposure considered are inhalation and ingestion which takes care of lead intake through air, food and fluids. The inhaled and ingested lead are absorbed in the lungs and the digestive tract respectively and deposited into the blood. The lungs and digestive tract model generates an inhomogeneous term in the model equation as will be seen in later section.

The blood represents the central compartment from where the incoming lead is distributed to other tissues. The blood also serves as indicator to predict concentration of lead in the critical or target organ. Lead in the central compartment exchanged directly with cortical bone, trabecular bone and soft tissues with the exchange being more rapid in cortical and trabecular bone than soft tissues.

The existing models for the systemic distribution and retention of lead were extended in the developed model to include transfer of lead to the compartment called breastmilk. The information used to model transfer to milk was based on a review of the available human and animal data (ICRP, 2001). If the volume of the milk produced per day was assumed to be 800 mL and blood volume is 2400 mL, the transfer rate from blood to milk was deduced to be 0.033 (800/2400 * milk:blood concentration ratio) where the milk:blood concentration ratio based on the experimental data is 0.1. There was a need to split the bone compartment into cortical and trabecular because the turnover of lead in the two bone types are different. It has been observed from literature that there is a more rapid turnover of lead in trabecular bone than cortical bone (Bert *et al.*, 1989)

In the model, the liver and the kidneys are lumped together with other soft tissues to reduce complexity. Soft tissues turn over more slowly than the blood. In some existing models like the Rabinowitz model, soft tissues were also lumped together.

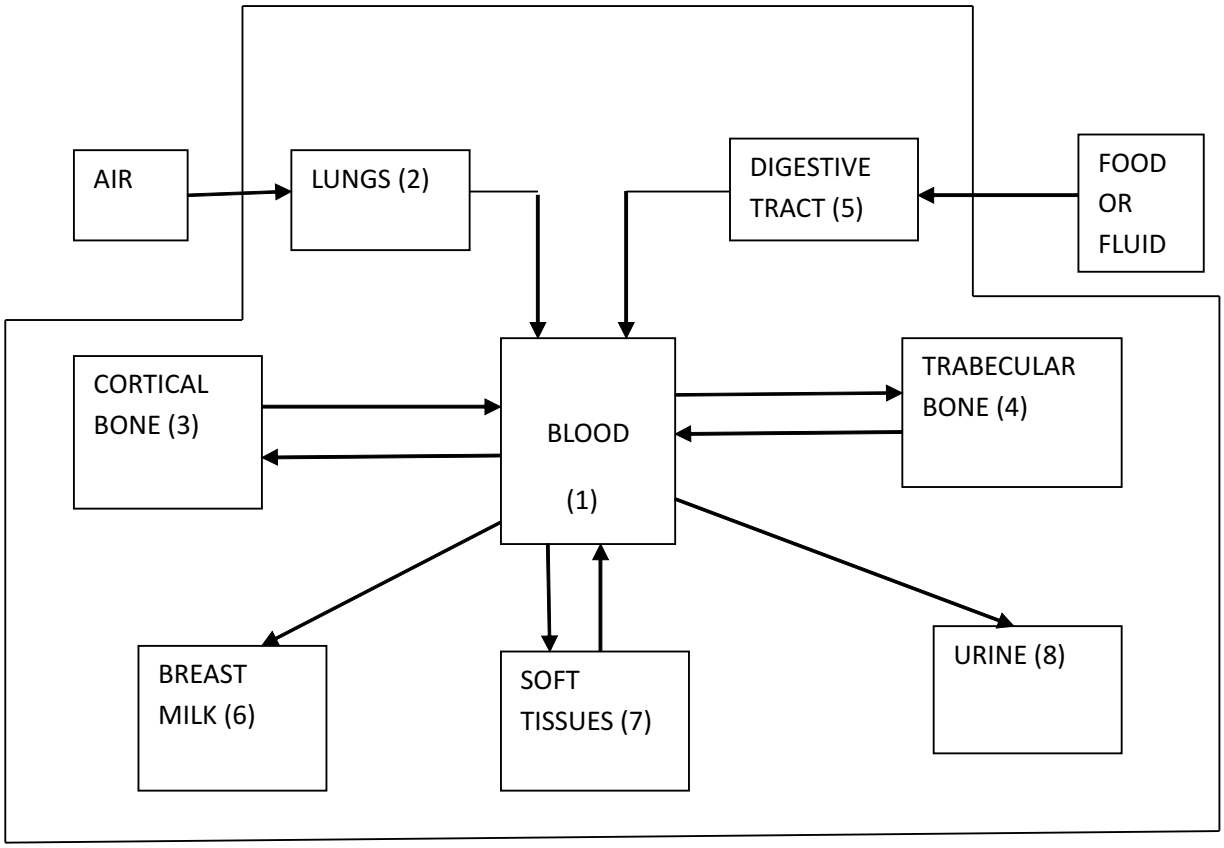

Figure 1: Conceptual Structure of Lead Model.

Computer Simulation

The formula used to describe the generated models was based on the fact that the rates of change of the concentrations of the elements of interest can be expressed in terms of a set of coupled first-order differential equation shown below;

$$\frac{dX_i}{dt} = \frac{A_i}{M_i} - K_i X_i + \sum_j K_{ji} X_j \frac{M_j}{M_i} \quad (1)$$

Where X_i is the concentration of elements in compartment i, M_i is the mass of compartment I, A_i is the rate at which elements enter compartment i directly from outside the body, K_i is the rate constants for the movement of elements either into or out of compartment i and is defined as the reciprocal of the mean residence time for lead in the compartment; j refers to each pool other than i. K_{ji} is the rate constant for movement from compartment j to i with the notation that;

$$K_i = \sum K_{ji} \quad j = 0 \quad (2)$$

The rate constants i.e. K's were considered to be independent of time and total element content in a compartment. Based on this study design, blood is the central compartment that receives lead directly from outside the body through either the lung or the gastrointestinal tract. For exchange between the central compartment (blood) and bone, for instance, equation (1) becomes

$$\frac{dX_{(blood)}}{dt} = \frac{A}{M_{(blood)}} - K_{(blood)} X_{(blood)} + \frac{M_{(bone)}}{M_{(blood)}} . K_{(bone,blood)} . X_{(bone)} \quad (3)$$

Likewise, exchange between bone and the blood is represented by the equation;

$$\frac{dX_{(bone)}}{dt} = \frac{M_{(blood)}}{M_{(bone)}} . K_{(blood,bone)} . X_{(blood)} - K_{(bone)} X_{(bone)} \quad (4)$$

It should be noted that the factor, $\frac{A}{M'}$ becomes zero since lead is not directly deposited into the bone from either the lungs or the gastrointestinal tract.

The differential equations for other

compartments can be written in like manner.
The lungs and digestive tract model generated an inhomogeneous term in the equation which is:

$$D = p\alpha + q\beta \quad (5)$$

Where α and β are the rates at which lead enters the lungs and digestive tracts respectively while p and q are proportionality constants (Batschelet *et al.*, 1979). D is the intake quantity from outside the body and it helped in modifying the intake rate under different conditions. It was assumed that the rate at which lead moves from the lungs to the blood was proportional to the rate at which lead enters the lungs (Y_{21}) i.e.

$$Y_{21} \propto \alpha$$
$$Y_{21} = p\alpha \quad (6)$$

Also, the rate at which lead enters the blood from the digestive tract was assumed to be proportional to the rate at which lead enters the digestive e tract (Y_{51}) i.e.

$$Y_{51} \propto \beta$$
$$Y_{51} = q\beta \quad (7)$$

The model developed was thereafter tested by inserting same data used by Rabinowitz *et al.*, (1976) and the outputs were compared.

Tissue lead levels before the onset of lactation i.e. in pregnancy was modeled to know the concentration of lead at delivery. The concentration of lead in the tissues at 0 day therefore represents the concentration at delivery which marks the beginning of lactation.

Parameter Estimation

In this study, parameters used for the various coefficients in the different equations were sourced from the literature. Parameters for the exchanges between blood, soft tissues, cortical bone and trabecular bone were derived from Bert *et al.,* 1989 while that of urine transfer was obtained from Rabinowitz *et al.,* 1976. Volume ratios were obtained from Legette, 1993 while blood to breastmilk transfer rate constant was derived from ICRP, 2001. The various values and their references are shown in Table 1. With appropriate values for individual body height and body weight as shown in Tables 2 and 3, the blood volume of each subject was derived. This helped in validating the new model developed in this study.

Computer Implementation

The equations constituting the physiologically-based kinetic model along with the input parameters were solved using the Waterloo Maple Software for conducting simulations. All computational solutions were produced using MAPLE 13 and its ODE solver. Coding for the model was verified to satisfy mass balance.

Table 1: Model Parameters for Lead Transfer

Parameters	Description
K_{12}=0.001835 (Bert *et al.*, 1989)	Rate constant for transfer from blood to soft tissue
K_{21}=0.00235 (Bert *et al.*, 1989)	Rate constant for transfer from soft tissue to blood
K_{13}=0.00578 (Bert *et al.*, 1989)	Rate constant for transfer from blood to Cortical bone
K_{31}=0.0000325 (Bert *et al.*, 1989)	Rate constant for transfer from C.B to blood
K_{14}=0.00240 (Bert *et al.*, 1989)	Blood to T.B transfer
K_{41}=0.00229 (Bert *et al.*, 1989)	T.B to blood transfer
K_{15}=0.033 (ICRP 2001)	Blood to Breastmilk transfer
K_{16}=0.0210 (Rabinowitz *et al.*, 1976)	Blood to urine transfer
ST to blood=0.67 (Legette, 1993)	Volume ratio of soft tissue to blood
CB to blood=0.05 (Legette, 1993)	Volume ratio of C.B to blood
T.B to blood=0.03 (Legette, 1993	Volume ratio of T.B to blood

Accuracy Check

As a way of checking this implementation, exposure data from Rabinowitz were inserted in the new model developed in this study and the outputs in the relevant tissues were similar to those published by Rabinowitz *et al.,* (1976) as shown in Figures 2a and 2b.

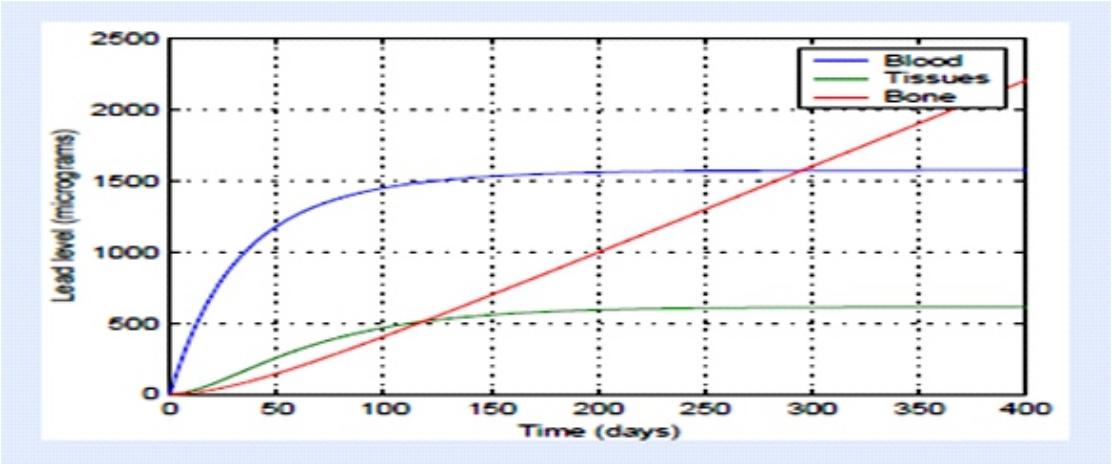

Figure 2a: Rabinowitz Prediction

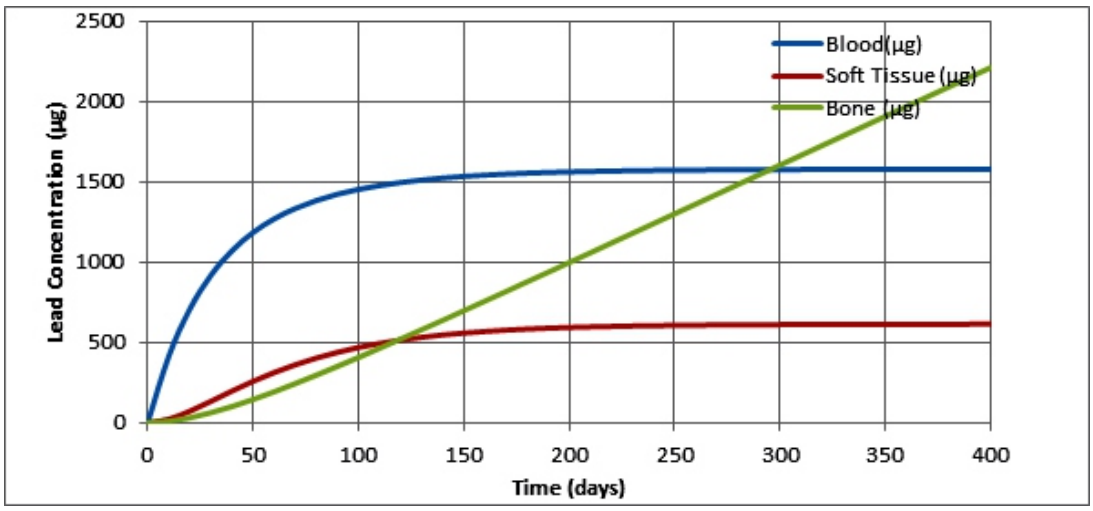

Figure 2b: New Model Prediction (Using Rabinowitz Data)

RESULTS AND DISCUSSION

Figure 3 shows that there is a significant increase in blood lead at delivery after which a gradual drop in the blood lead level is observed within the first 100 days. Equilibration takes place by the 200th day. The initial drop in the blood lead may be as a result of exclusive breastfeeding within the first 100 days as it has been reported that all studies show rapid increase in milk production and consumption during the first few weeks after birth, followed by a slower increase over the subsequent months (Neville *et al.*, 1988). Breast milk intake by the baby is reduced significantly in later months since some other range of foods are introduced to the baby and this appears to be the situation throughout the period of lactation. This may be responsible for the increase observed in blood lead by the 24th week (168 days) of lactation. It should however be noted that 0.033 (ICRP, 2001) was used as a reasonable value of rate constant to model the transfer of lead from blood to breastmilk.

The milk to blood ratio of lead was predicted by the model developed in this study (Figure 3 being the simulation output) to be 0.3 which agrees with Moore (1983) prediction. [Blood Lead Level (BLL) = 2145 µg while Milk Lead Level (MLL) = 576 µg]. The model predicted 63% increase in blood lead in lactation while pregnancy scenario predicts 26%. This is in agreement with Mushak (2003) who predicted 41-99% increase in bone turnover during lactation and more than 30% in pregnant women. This also confirms that mobilization of lead from maternal bone into blood is more in lactation than in pregnancy (Gulson *et al.*, 1998). It is however pertinent to consider various scenarios for bone mobilization by introducing the Heaviside functions into the model equations.

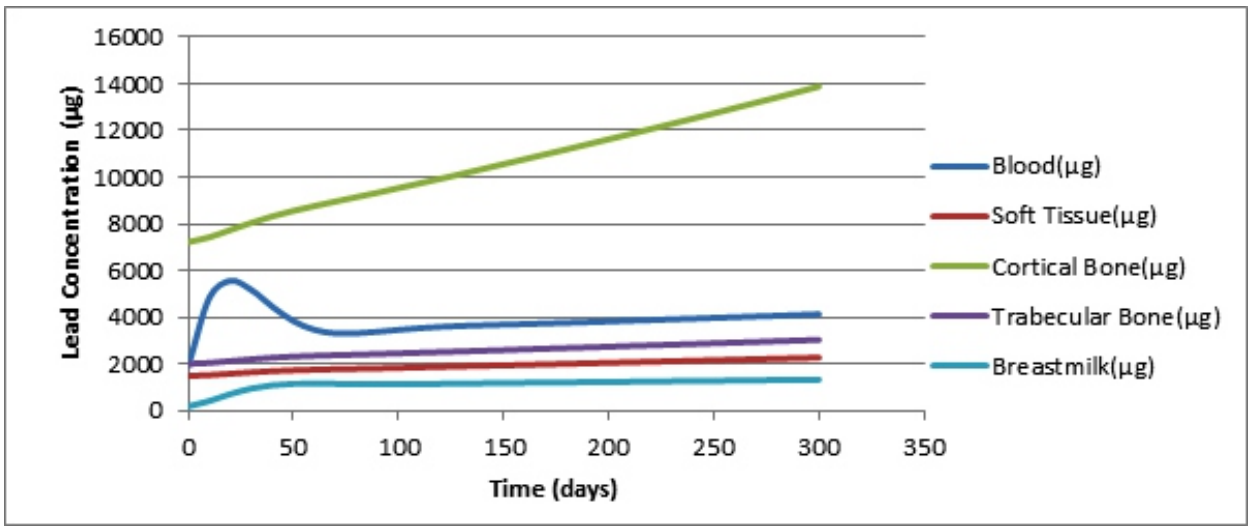

Figure 3: Tissue Lead Levels during Lactation (Blood Lead Level at Delivery = 2145 micrograms)

If it is assumed that the subjects move to a rural area after 100 days as shown in Figure 4, the value of intake quantity from outside the body (D) is changed. The lead level of the body is reduced, but some quantity of lead is ingested by the step function (i.e. Heaviside function) where t is the time in days. As a reasonable value, the intake rate is reduced from 49.3 to 33 (Borrelli and Coleman, 1997). D is therefore defined as;

$$D = 49.3 * Heaviside(100 - t) + 33 * Heaviside(t - 100) \quad (8)$$

Where t is time in days.

The blood lead level was found to decrease to 43 µg/dl from 274 µg/dl while the milk lead level decreased to 15 µg/dl from 81µg/dl.

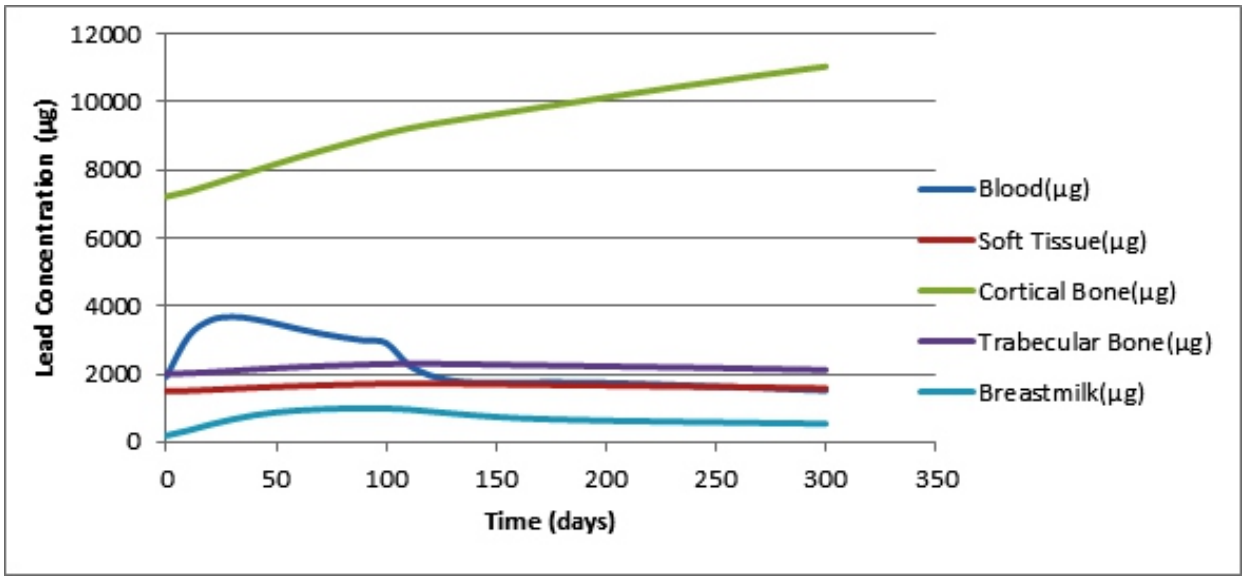

Figure 4: Tissue Lead Levels in Subjects Living in Low Lead Environment

Assuming that the subjects stay in the same area of high lead contamination, but decide to take medication (chelation therapy) to reduce the lead level in the body after 100 days, the medication works to remove the lead through the urine. This affects the coefficient of urine in the differential equation and indirectly the blood coefficient. The coefficient of urine is therefore increased from 0.0210 to 0.210 (Batschelet *et al.*, 1979). The differential equation for blood could therefore be rewritten as;

$$\frac{d(BL)}{dt} = (0.0210 * Heaviside(100 - t) + 0.210 * Heaviside(t - 100)) * BL(t) \quad (9)$$

Drastic drop in the blood and tissue lead levels is observed when the subject is massively chelated after 100 days as shown in Figure 5. Blood lead level drops from 274 µg/dl to 58 µg/dl while the milk lead level decreases to 24 µg/dl from 81 µg/dl. Massive chelation may however be harmful to the subjects.

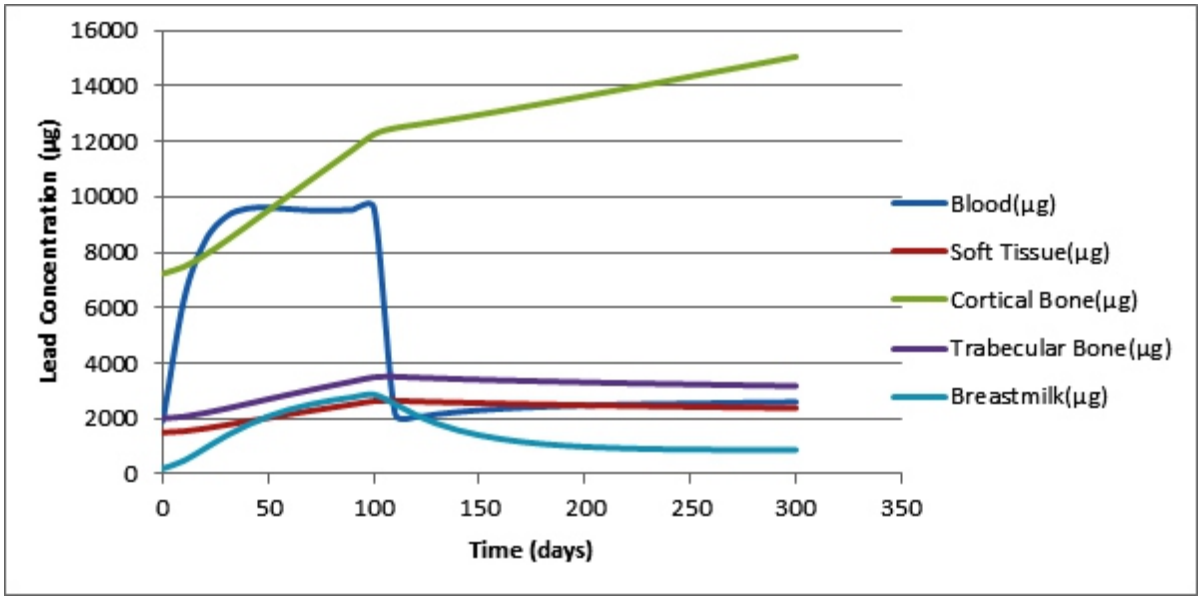

Figure 5: Tissue Lead Levels in Subjects Massively chelated

With a safer medication such as the use of chelating agents like calcium, the value of the urine coefficient is reasonably reduced to 0.0316 (Batschelet *et al.*, 1979). The equation now becomes;

$$\frac{d(BL)}{dt} = \big(0.0210 * Heaviside(100 - t) + 0.0316 * Heaviside(t - 100)\big) * BL(t) \quad (10)$$

Low medication also gives a notable drop in blood lead levels after 100 days as shown in Figure 6 which is safer for the subjects (Batschelet *et al.*, 1979). The blood lead level drops to 154 µg/dl from 274 µg/dl while the milk lead level drops from 81 µg/dl to 58 µg/dl.

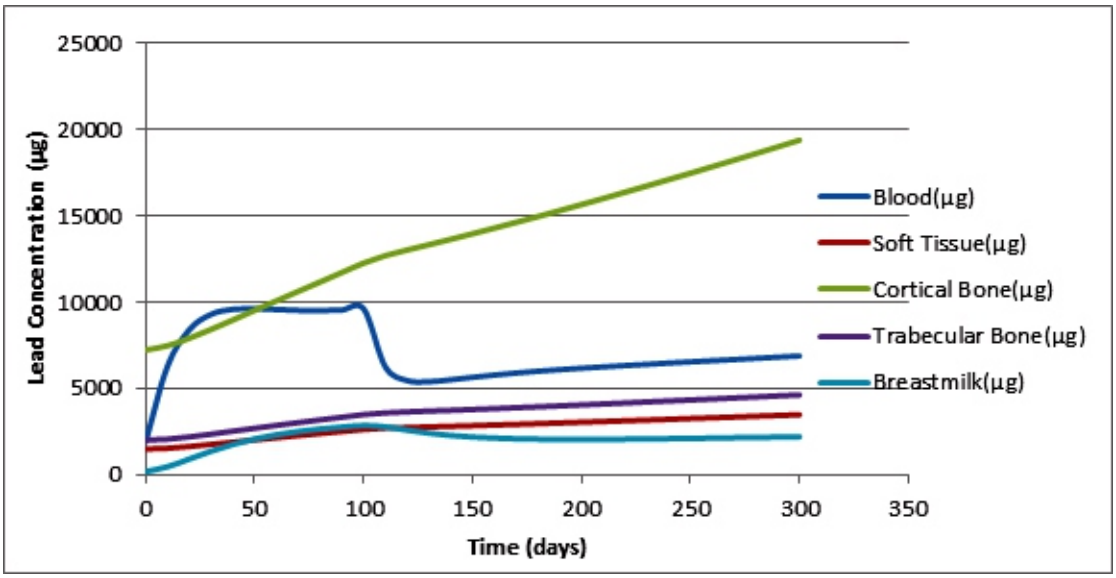

Figure 6: Tissue Lead Levels in Subjects with Low Medication

Comparing the effects of moving the subjects to a low lead environment and giving them safer medication, the model predicts that it is better the subjects stay in low lead environment than being chelated. The model predictions also show that the permissible lead level of 10 µg/dl is surpassed even under various scenarios for the highly exposed subjects.

The pattern of blood lead concentration confirmed across pregnancy as shown in Figure 7 is similar to Hertz and Rothenberg's observations (Rothenberg *et al.,* 1994; Hertz *et al.*, 2000;).

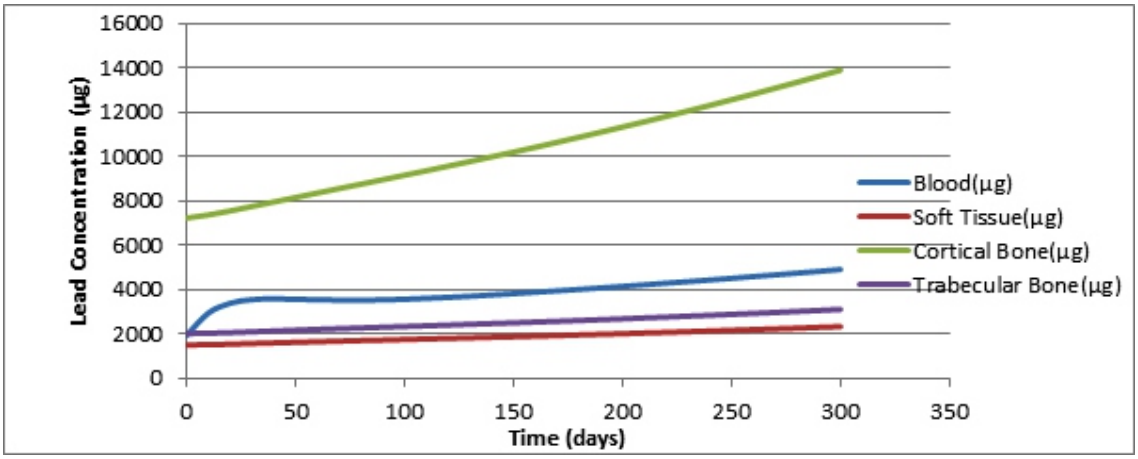

Figure 7: Lead Levels in Pregnancy.

Table 2: Model Validation for High Exposure [Air= 75 µg/m^3 (UNEP, 2011), Food=1220 mg/kg (Abdu and Yusuf, 2013)]

					BLOOD LEAD LEVEL		MILK LEAD LEVEL	
ID	AGE	Weight (Kg)	Height (cm)	Blood Volume(dl)	...	Measured (µg/dl)	Predicted (µg/dl)	Measured (µg/dl)
1		44	159	30.7	59.6	48.7	3.6	2.9
2		41	157	29.2	49.6	67.7	3.7	2.8
3		44	157	30.2	50.3	53.4	3.6	1.9
4		44	155	29.6	59.0	61.0	3.7	3.9
5	20	66	169	40.9	38.3	38.8	0.8	0.8
6	30	72	166	41.9	44.0	38.1	5.8	8.6
7	32	59	167	37.9	63.1	46.4	2.8	1.1
8	18	55	145	30.9	75.0	64.6	3.6	6.4
9	25	62	155	35.6	83.4	79.9	3.1	NA
10	25	51	149	30.5	65.6	86.8	3.6	2.7
11	25	62	152	34.8	55.6	51.5	3.1	3.3
12	20	50	155	31.6	33.1	28.2	2.7	1.9
13		NA	NA	NA	NA	83.7	NA	11.1
14	38	69	158	38.7	91.7	84.0	2.8	3.9
15	20	62	156	35.9	70.6	65.1	3.0	4.0
16	36	85	171	47.8	46.5	65.9	2.3	3.2
17	20	NA	NA	NA	NA	57.5	NA	13.9
18	30	88	169	48.1	65.3	60.4	2.3	3.8
19	NA	NA	NA	NA	NA	67.3	NA	6.3
20	22	54	165	35.7	65.6	79.4	0.3	0.2
21	37	74	158	40.4	51.5	47.4	0.8	0.8
22	30	83	163	44.7	42.5	41.0	0.8	0.5
23	37	98	170	51.7	60.5	56.3	3.2	4.7
24	30	71	171	43.1	34.6	23.9	9.5	9.6
25	26	52	NA	33.8	36.7	31.3	3.2	2.2
26	30	94	NA	61.1	70.4	68.2	5.1	5.0
27		NA	NA	NA	NA	75.6	NA	12.0
					Chi = 0.0056, r=0.557 at 0.01 sig level		Chi= 0.998 , r=0.863 at 0.01 sig level	

Table 3: Model Validation for Low Exposure [Air=8.09 μg/m^3 (Obioh *et al.,* 2005), Food=60.2 mg/kg (Okoya *et al.,* 2011)]

					MILK LEAD LEVEL		BLOOD LEAD LEVEL	
ID	Age	Weight (Kg)	Height (cm)	Blood Volume (dl)	Predicted (μg/dl)	Measured (μg/dl)	Predicted (μg/dl)	Measured (μg/dl)
1	41	71.7	156.5	39.2	0.26	BDL	6.7	3.7
2	25	63.4	157	36.6	0.38	0.2	7.4	5.2
3	33	46.5	152	29.7	1.2	0.2	6.5	3.7
4	28	57.4	161	35.7	0.6	0.1	10.4	7.4
5	35	55.9	159	34.6	0.6	0.1	10.0	9.8
6	38	63.7	154	35.9	0.5	0.1	13.5	9.9
7	40	43.4	143	26.6	1.6	0.2	14.6	9.9
8	28	56.5	160	35.1	0.5	0.1	9.0	9.1
9	32	50	150	30.3	1.03	0.1	10.5	8.7
10	30	42	144.5	26.5	1.6	0.1	10.6	10.8
11	21	57	144	31.3	0.8	0.3	14.5	12.4
12	14	75	145	37.5	0.2	NA	16.3	13.1
13	20	52	153	31.8	0.8	0.2	9.7	7.9
14	31	45	139	26.2	0.5	0.2	11.5	9.6
15	30	50	158	32.4	0.8	NA	8.0	7.1
16	31	51	149	30.5	1.0	0.4	24.5	37.9
17	29	70	158	39.0	0.2	NA	7.4	6.5
18	29	45	144	27.4	1.4	NA	12.5	10.6
19	23	42	145	26.6	1.5	0.1	14.2	10.8
20	22	52	155	32.3	0.7	NA	13.1	7.2
21	40	NA	NA	NA	NA	0.3	NA	NA
22	22	53	157	33.1	0.7	0.3	9.5	NA
23	30	59	159	35.7	0.5	NA	7.5	8.1
24	32	49	151	30.3	1.0	0.4	13.3	8.2
25	19	48	149	29.5	1.0	0.4	13.4	9.8
26	27	80.6	145	39.4	0.2	0.1	11.2	11.2
27	20	50.4	152.5	31.1	0.9	NA	11.6	9.9
28	27	56	146	31.4	0.9	NA	11.7	11.2
29	31	40.7	148	46.8	1.5	0.7	9.9	6.5
30	30	89	158	45.3	0.2	0.1	12.5	12.8
31	35	65	156	36.9	2.4	2.4	6.7	11.1
32	34	60.3	157	35.6	0.5	NA	7.8	8.9
33	23	50.3	154	31.5	0.8	NA	11.3	7.3
34	28	60.4	154.5	34.9	0.5	NA	8.1	10.2
35	26	50	147	29.7	1.0	0.3	13.8	9.8
36	35	63	165	38.7	0.2	0.4	5.2	5.5
37	23	55	147.5	31.5	0.8	0.4	11.3	6.2
38	NA	73	157	39.8	NA	0.4	NA	8.7
39	20	55	153	32.8	0.7	0.3	9.7	12.6
40	22	62	150	34.4	0.5	1.0	8.2	7.4
41	21	98	161	49.1	0.4	0.3	10.7	9.7
42	24	61	160	36.6	0.4	0.8	6.3	10.1
43	23	50	143	28.8	1.2	NA	14.7	11.1
44	NA	68	145	35.2	NA	0.3	NA	6.7
45	31	55	163	35.6	0.5	NA	7.6	8.4
46	35	74	151.5	38.7	0.2	0.8	5.2	11.4
47	20	63	155	35.9	0.4	0.3	6.7	6.7
48	22	49	141.5	28.1	1.2	NA	15.6	8.4
49	20	56	150.5	32.5	0.7	0.6	10.0	9.5
50	29	65	147	34.6	0.6	0.2	8.4	13.6
					Chi = 4.87E-07 (Bad fit), r=0.4379 at 0.01 sig level		Chi= 0.0086, r=0.7851 at 0.01 sig. level	

When the predicted and measured values of blood and milk lead concentrations were compared, the chi square results showed there is a fairly good correlation between the predicted and measured blood lead concentrations for the highly exposed subjects as shown in Table 2. A fairly good correlation also exists between the predicted and measured blood lead concentrations for subjects with reduced lead exposure as shown in Table 3. It was however observed that the correlation between the predicted and measured milk lead levels for the two study areas were bad especially in subjects with reduced exposure to lead.

CONCLUSION

The model developed in this study predicted that mobilization of lead from maternal bone to blood is more in lactation (63%) than in pregnancy

(26%). This confirms that lactation is associated with a marked increase in bone turnover. Thus, bone lead constitutes an important threat, not only to women with ongoing environmental exposures but also to women enjoying reduced environmental exposures but who have had elevated exposures in the past. In this regard, most women of child bearing age in Nigeria are still considerably susceptible to the effects of past lead exposure. Also, this proves that breastfed infants are at high risk of lead exposure during lactation because most of the lead in breastmilk gets to them as it has been encouraged that breastmilk should be emptied through breastfeeding daily so that production of milk can increase (Butte and King, 2005).

It was also observed from the new model validation that fairly good correlation exists between the predicted and measured blood lead level for the two study areas as shown in Tables 2 and 3. There was however no good agreement between the predicted and measured milk lead levels especially for subjects with reduced lead exposure.

It can therefore be concluded that using systems of first order differential equations helps in the analysis of lead kinetics inside the body, thus making it an effective tool in kinetic modeling which can be viewed as dynamic constructs that can be continually updated as significant new information and data become available.

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