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A human pregnancy PBBK model for lead, mercury and selenium

Danjuma. D. Maza *, Joshua. O. Ojo
Department of Physics and Engineering Physics Obafemi Awolowo University, Ile-Ife,
Corresponding Author: Danjuma. D. Maza

Abstract: *A human physiologically-based biokinetic (PBBK) model for the trio mixture of mercury, lead and selenium which was developed in an earlier study has been modified into a mixture model for a pregnant mother/fetus. The modified model was capable of simultaneously simulating the absorption, distribution, metabolism, and elimination (ADME) properties of these three elements in a pregnant mother and her fetus. This model consists of three pairs (a pair for each of the elements, lead, mercury and selenium) of maternal/fetal models which were integrated into a single model. This model was adapted and employed to investigate the health risk posed to a pregnant mother and her fetus due to simultaneous exposure of the pregnant mother to these elements. The health risk index (HRI) to three organs (brain, liver and kidney) of the mother and two organs (brain and liver) of the fetus were simulated. The simulated HRI were for a pregnant mother presumed to have consumed contaminated cereals from a contaminated mining village (Bagega in nothern Nigeria). Two scenarios were assumed namely; (a) adequate selenium intake (2.5 µmol /kg/day), and (b) high selenium intake (7.5 µmol /kg/day). Mercury and lead input doses were calculated as 1773.077 µmol /kg/day and 3361.534 µmol /kg/day, respectively. A continuous exposure, for the entire period of gestation was simulated. For the two scenarios simulated, the HRI for the brain, liver and kidney of the pregnant mother were all high throughout the gestation period. The liver and kidney of the pregnant mother appeared to be particularly at risk in the second trimester. The results also showed that even with adequate or high selenium intake by a pregnant mother, the consumption of these contaminated cereals from Bagega could put the brain and liver of the fetus at risk, particularly within the first two months of gestation.*

Key Words*: physiologically-based, biokinetic, interaction, pregnancy, mother, fetus*.

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I. Introduction

Physiologically-based biokinetic (PBBK) models have been useful tools in quantifying human exposure to environmental pollutants. Their usefulness in this regard is derived from the fact that, using physiological and biochemical data, the absorption, distribution, metabolism and elimination (ADME) properties of chemical pollutants in animals and humans can be described quantitatively (Andersen et al., 1987; Ruiz et al., 2011; Campbell et al., 2012; Maza and Ojo, 2016). Additionally, physiologically-based biokinetic models can equally be used to predict internal tissue doses of environmental pollutants during pregnancy in both the mother and fetus. For a wide variety of environmental pollutants and pharmaceutical drugs, several PBBK models have been developed to describe their fate in the fetus due to maternal exposure (Gray, 1995; Lueke et al., 1997; Gentry, 2003; Gentry, 2008; Gaohua et al., 2012).

The toxic effects of lead and mercury to humans and animals is well studied and documented (Apostoli et al., 1998; Lyn, 2002; Farhana et al., 2005; Mark and Houston, 2011; Robin, 2012; Flora et al., 2012). The mitigating role of selenium to the toxic effects of these toxic elements is equally well studied and documented (Baoyan and Xuelin, 2000; Hamilton, 2004; Ani et al., 2006; Deore et al., 2007). In an attempt to model the combined effect of mercury and lead on selenium, an adult physiologically-based biokinetic model was developed for the trio mixture or mercury, lead and selenium (Maza and Ojo, 2017), to simulate, simultaneously the ADME properties of mercury, lead and selenium in some critical organs of adult humans.

The susceptibility of individuals to the toxic effects of environmental pollutants is expected to vary from person to person. Pregnant mothers, lactating mothers, infants and the elderly are categories of individuals who seem to be more susceptible to some toxic effects of mercury and lead.

The focus of the present study is to modify the existing adult model for the trio mixture of mercury, lead and selenium (Maza and Ojo, 2017), to simulate simultaneously the ADME properties of mercury, lead and selenium in a pregnant mother and her fetus. Furthermore, the present study is equally geared towards adapting and applying the modified model to estimate the possible risk to pregnant women and their fetuses which may result from the consumption of contaminated cereals from Bagega village of Anka L.G.A, Zamfara State, Nigeria. Bagega is one of the villages involved in the Zamfara lead poisoning episode which occurred in 2009 (Yahaya et al., 2015).

In a previous study undertaken by us (Maza and Ojo, 2018) a hypothesis was proposed for the estimation of the health risk index (HRI), associated with the co-exposure to mercury, lead, and selenium. The hypothesis defines, the health risk index in tissue, T, due to simultaneous exposure to mercury and lead, in the presence of selenium as:

$$HRI_{HgPbT} = \frac{C_{HgT} + C_{PbT}}{C_{SeT}} \quad (1)$$

Where C_{HgT}, C_{PbT} and C_{SeT} are the molar concentrations of Hg, Pb and Se in tissue T, respectively.

II. Methods

The model was developed as a modification to an existing model, a human pbbk model for the trio mixture of lead mercury and selenium, (Maza and Ojo, 2017). The present model is an integration of three pairs of maternal/fetal models: a pair (shown in Figure 1) for each of the elements, lead, mercury and selenium. The interaction between these elements was modelled by modifying the partition coefficient of each element in respective tissues in a similar fashion to the existing adult model. The three pairs of models were integrated using the same logic and dose categorization employed in the existing models (Maza and Ojo, 2017; Maza and Ojo, 2018). In developing the logic, the result of studies carried out on rats by Ralston and co-researchers (Ralston and Raymond, 2008; Ralston et al., 2008) was used as guide. The model was then adapted and used to estimate the HRI_{HgPbT} of the brain, liver and kidney of a pregnant mother, and of the brain and liver of the fetus. The model was coded using Maple software simulation language.

2.1. Additional Compartments/Changing Maternal Tissue Volumes During Pregnancy

In addition to all the compartments in the existing adult model for the trio mixture of mercury, lead and selenium (Maza and Ojo, 2017), the placenta was included as a compartment in each maternal model. All tissue volumes and blood flow rates in the maternal models, except richly-perfused tissues, placenta and fat, were modelled as constant fractions of body weight. Changes in the physiology of the pregnant woman are particularly accompanied by changes to her blood volume, mammary gland, uterus, and fat. In the current model the mammary gland, and the uterus were not represented as distinct compartments, however, changes to their volumes were reflected as changes to the volume of the richly-perfused tissues. Thus, in the present modelthe volume of richly-perfused tissues, placenta and fat were modelled as time-dependent parameters.

The time-dependent volumes of the mammary gland, fat and uterus were described by the following equations in the maternal models (Yoon et al., 2011):

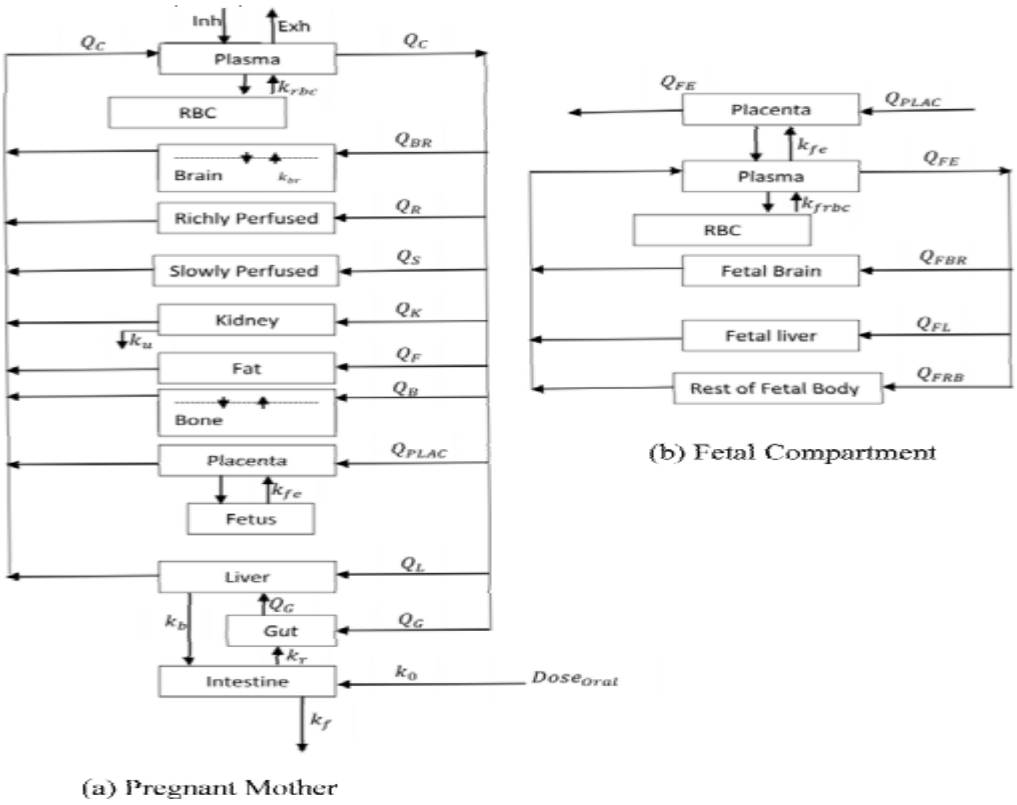

Figure 1. A pair of maternal/fetal models

$V_{MG} = BW_0 \left(V_{M0F} + 0.0065e^{(-7.44e^{-0.00068\,GT})}\right)$ (2)

$V_{FG} = BW_0(V_{F0F} + 0.09e^{(-12.91e^{-0.00080\,GT})})$ (3)

$V_{UG} = BW_0(V_{U0F} + 0.02e^{(-4.72e^{-0.00038\,GT})})$ (4)

Where V_{MG}, V_{FG} and V_{UG} are the volumes of mammary gland, uterus and fat, respectively, during gestation. While V_{F0F}, V_{M0F}, V_{U0F}, are the pre-pregnancy fractional volumes of mammary gland, fat, and uterus respectively. BW_0 is the pre-pregnancy body weight and GT is gestation time in hours.

Abduljalil et al., (2012) described the plasma and red blood cell volumes, during pregnancy, for a woman weighing 61.1 kg (pre-pregnancy) by the following equations:

$V_P = 2.5 - 0.223GW + 0.00042GW^2 - 0.00007GW^3$ (5)

$V_{RBC} = 1.49 + 0.0098GW$ (6)

By introducing normalizing factors, Equations 5 and 6 were modified to give the plasma and red blood cell volumes during pregnancy respectively as:

$V_{PG} = \frac{V_{P0}}{2.5}(V_P = 2.5 - 0.223GW + 0.00042GW^2 - 0.00007GW^3)$ (7)

$V_{RBCG} = \frac{V_{RBC\,0}}{1.49}(1.49 + 0.0098GW)$ (8)

Where V_{PG} and V_{RBCG} are plasma volume and red blood cells volume respectively, while V_{P0} and V_{RBC0} are pre-pregnancy volumes of plasma and red blood cells respectively and GW is the gestation age in weeks.

2.2. Changes in Maternal Blood Flow Rates

During gestation, the blood flow rate to tissues such as mammary gland, uterus, and fat, whose volumes were modelled as time-dependent parameters, were also modelled as time-dependent parameters. It was assumed that the increase in blood flow rate to these tissues were proportional to the increase in their respective volumes (Gentry et al., 2003; Yoon et al., 2011). Thus, the changes in blood flow rate to the mammary gland, fat and uterus were respectively modelled as:

$$\Delta Q_{MG} = \frac{Q_{M0}\Delta V_{MG}}{V_{M0}} \quad (9)$$

$\Delta Q_{FG} = \frac{Q_{F0}\Delta V_{FG}}{V_{F0}}$ (10)

$\Delta Q_{UG} = \frac{Q_{U0}\Delta V_{UG}}{V_{U0}}$ (11)

Where, ΔQ_{MG}, ΔQ_{FG}, and ΔQ_{UG} are the time-dependent changes in the blood flow rates to the mammary gland, fat and uterus respectively. ΔV_{MG}, ΔV_{FG}, and ΔV_{UG}, being time-dependent changes to the volume of mammary gland, fat and uterus respectively. While, Q_{M0}, Q_{F0}, Q_{U0}, are the pre-pregnancy blood flow rates to the mammary gland, fat and uterus respectively. And V_{M0}, V_{F0}, and V_{U0}, respectively, are pre-pregnancy volumes of mammary gland, fat and uterus.

2.3. Fetal Models

Specific fetal tissues that were modelled in this work were the liver, brain, plasma and red blood cells. The rest of the body tissues were lumped together as one compartment. The equations describing fetal body weight, placenta volume, fetal plasma volume, and fetal red blood cells volume were adapted from (Shipp et al., 2000).

Fetal weight, BW_F, was described by:

$$BW_F = 3.50e^{(-16.08e^{(-0.000567\,GT)})} + 3.50e^{(-140.2e^{(-0.000701\,GT)})} \quad (12)$$

The placenta volume, V_{PLAC}, was given as:

$V_{PLAC} = 0.85e^{(-9.434e^{-0.000523\,GT})}$ (13)

Time-dependent fetal brain volume, V_{BRF}, was described by:

$V_{BRF} = 0.50e^{(20.93e^{-0.000619\,GT})}$ (14)

Fetal liver volume, V_{LF} was modelled as percentage of fetal body weight. i.e.:

$V_{LF} = 0.037BW_F$ (15)

Fetal plasma volume, V_{PF}, and red blood cells volume, V_{RBCF}, were modelled as fractions of fetal body weight, thus:

$V_{PF} = 0.0425BW_F$ (16)

$V_{RBCF} = 0.0245BW_F$ (17)

The rest of the fetal body volume was calculated as the difference between the total fetal body weight and the volumes of the liver and brain.

Based on research efforts of Kiserud et al. (2006) and Yoon et al. (2011), the total cardiac output for the fetus and placenta blood flow were respectively calculated as:

$Q_F = \frac{2}{3}Q_{CI}BW_F$ (18)

$$Q_{PLAC} = \frac{1}{3} Q_{CI} BW_F \quad (19)$$

Where Q_{CI}, Q_F, and Q_{PLAC} are the cardiac index, total cardiac output for the fetus and placenta blood flowrespectively. The cardiac index, $Q_{CI} = 24$ L/kg/hr.

Blood flow to the fetal brain and liver were calculated as 0.3 and 0.36 of the total cardiac output respectively, while the difference between the total cardiac output and the blood flow to the brain and liver goes to the rest of the fetal body.

2.4. Simulation

The health risk index of the brain, liver and kidney of a pregnant mother were simulated along with the HRI of the brain and liver of her fetus. The simulations were for a pregnant mother having a pre-pregnancy weight of 65kg, presumed to be living in Bagega, a polluted mining community in Nigeria. It was assumed that the pregnant mother consumed approximately 0.25kg daily of each of locally produced cereals (maize, rice and sorghum) for the period of the simulation. The concentration of mercury and lead in these cereals were extracted from the work of Yahaya et al. (2015. The simulations were based on two assumed selenium intake, namely; (a) adequate selenium intake (2.5 µmol /kg/day), and (b) high selenium intake (7.5 µmol /kg/day). Input doses for Mercury and lead were calculated as 1773.077 µmol /kg/day and 3361.534 µmol /kg/day, respectively, using the same formula employed in our previuos work (Maza and Ojo, 2018). The simulations were for a continuous exposure, for the entire period of gestation (270 days).

III. Results and Discussion

Presented in Fig. 2 to Fig. 6 are the results of the simulation, showing the health risk indices against time for some critical organs of the pregnant mother (presumed to have consumed contaminated cereals during the period of simulation) and the fetus. For ease of comparism, the simulation for the two scenarios, based on selenium intake (adequate selenium intake and high selenium intake), were stacked together. The simulations in Fig. 2, Fig. 3 and Fig. 4 are the simulations for the brain, liver and kidney of the pregnant mother respectively, while Fig. 5 and Fig. 6 are the simulations for the brain and liver of the fetus respectively.

3.1. Health Risk Indices of the Pregnant Mother

The results (Fig. 2 to Fig. 4) showed that the HRI of the three tissues under investigation were all high for the two scenarios simulated. With adequate selenium intake, the HRI for the liver and kidney (Fig. 3a and Fig. 4a) of the pregnant mother were high throughout the gestation period, having peaks of 80 and 11.5, respectively, in the trimester. These peaks reduced significantly to 12.1 and 1.2, respectively, when selenium intake was high. Furthermore, these peaks are substantially higher than what was simulated in our earlier study (Maza and Ojo, 2018) for a non-pregnant individual under similar scenarios (see TABLE 1 for comparison).

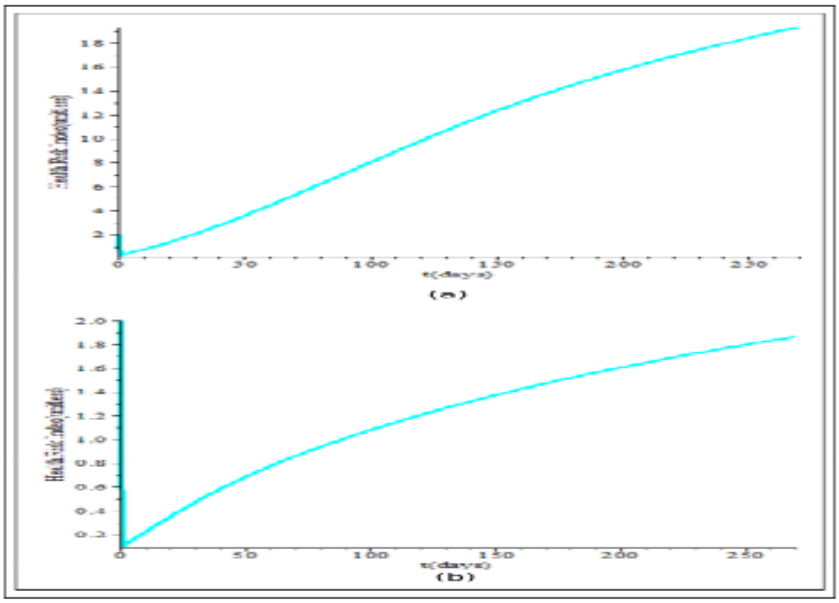

Figure 2 Health risk index in the brain of a pregnant mother

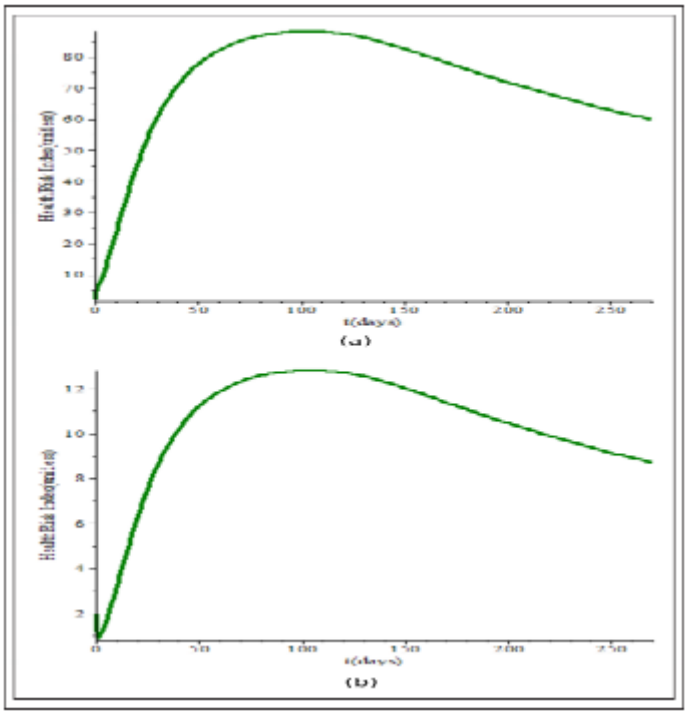

Figure 3: Health risk index in the liver of a pregnant mother

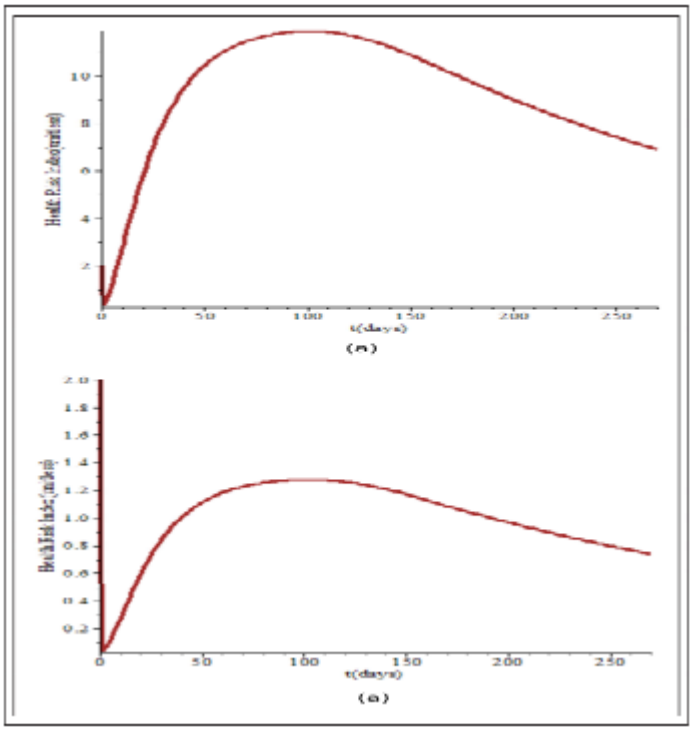

Figure 4: Health risk index in the kidney of pregnant mother

Table 1: Compares HRI in critical tissues of mother in present and previous study

	Previous study		Present Study	
Se intake	Liver HRI	Kidney HRI	Liver HRI	Kidney HRI
Adequate	12.15	1.5	80.0	11.5
High	1.7	0.17	12.0	1.2

3.2. Health Risk Indices of the Fetus

For both scenarios, Fig. 5 and Fig. 6 the HRI for the brain and liver were all high within the first two months of gestation, with a sharp peak occurring within the first few days. This suggests that even with adequate or high selenium intake by a pregnant mother, the consumption of cereals from Bagega could put the brain and liver of the fetus at risk, particularly within the first two months.

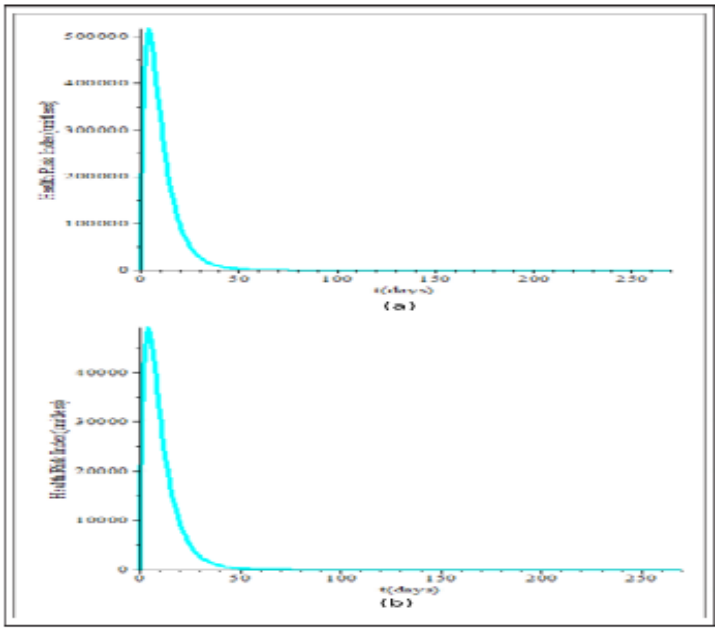

Figure 5: Health risk index in the fetal brain

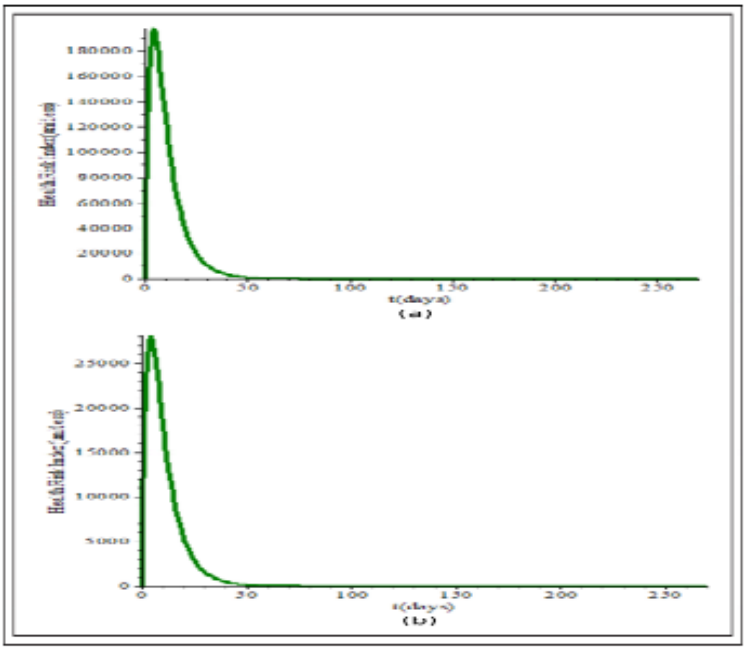

Figure 6: Health risk index in the fetal liver

IV. Conclusion

A human physiologically-based biokinetic mixture (mixture of lead, mercury and selenium) model was developed for a pregnant woman and her fetus. This model could simultaneously simulate, under various exposure scenarios, the absorption, distribution, metabolism and elimination (ADME) properties of lead, mercury and selenium in a pregnant woman and in the fetus. The model also simulated the health risk index to the brain, liver, and kidney of a pregnant woman who supposedly consumed contaminated cereals from Bagega. The study concluded that even with adequate or high selenium intake, the consumption of contaminated cereals from Bagega (a mining community in Nigeria) could still leave a pregnant woman in great danger, particularly

in the second trimester. It was further concluded that the consumption of these contaminated cereals by a pregnant woman will be particularly harmful to the fetus within the first two months of gestation.

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