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Simulation of Blood Lead Levels in Pregnant and Lactating Women in Osun State, Nigeria, Two Decades after Phase-out of Leaded Petrol

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Abstract

Elevated Blood Lead Levels (BLL) during pregnancy and lactation is known to be due to endogenous release of lead from its main storage sites in the human body – the cortical bones (with half-life of 27 years) and the trabecular bones (with half-life of 16 years). This release is due to the co-mobilization of lead together with calcium which is sourced from the bones during these periods of high requirement for calcium. While the level of such lead might be inconsequential for the mother, it could constitute a significant neurological and developmental health risk to the baby. In this work, employing a Physiologically Based Kinetic Model previously developed by us, we estimated expected current BLL in pregnant and lactating women who had had various levels of exposure to leaded petrol before its 2003 phase-out in Nigeria. Our results show that subjects born and raised in Osun state, Nigeria before 1996 and who had consequently been exposed to leaded petrol for a minimum of 8 years before its phase-out, will today have blood lead levels greater than the interventional level of 5 µg/dL recommended by the US Department of Human and Health Services for pregnant women. This is a conservative assessment, and has not taken into consideration additional ongoing lead intakes from diet and other exposure sources, such as from artisanal gold mining. This result therefore suggests that women aged 29 years and above will, during pregnancy and lactation, significantly benefit from interventions to mitigate endogenous lead release, for example via dietary calcium supplementation.

Keywords: Physiologically Based Kinetic Modeling. Blood Lead, Leaded petrol.

INTRODUCTION

Lead exposure remains a major public health concern as a result of the risks it poses, especially to women of child-bearing age and children. Exposure to lead accounts for 0.2% of all deaths and 0.6% of all disability adjusted life years (DALYs) globally (Mahuta, 2020). Before now, organic lead compounds such as tetraethyl lead and tetramethyl lead were added to gasoline to serve as an anti-knock agent and almost 75% of this is emitted as particulates from vehicle exhaust (Mahuta, 2020) which can be inhaled directly or ingested through food and water intake. However, the United States Environmental Protection Agency (USEPA) mandated the elimination of leaded gasoline by the end of 1996 which has been instrumental in reducing environmental lead concentrations globally. This was evident in a study conducted in Ile-Ife, Nigeria (post phase-out in 2003) which showed a marked decrease in blood lead levels of female subjects who were occupationally exposed to vehicular pollution; close to 50% BLL reduction was observed when compared to similar study done by the same authors in the 1990s (Ojo *et al*., 2007). Also, World Health Organization reported a BLL reduction ranging from 30-48% over a five-year period post phase-out in various countries (WHO, 2004). Unlike other carcinogens such as pesticides and radioactive materials, lead is not biodegradable as it does not vaporize nor disappear over time. Hence, most of the effects of leaded gasoline used over two decades ago is still being felt as people are still being exposed exogenously (through air,

food and water) and endogenously (through the release of stored lead in bones to blood). Endogenous exposure is being facilitated as a result of the affinity lead has for bones. Lead replaces calcium in bones and this houses 70 to 80% of absorbed lead in children, compared to 90 to 95% in adults (Ambrose *et al*., 2000). It is possible for lead to remain stored in the bones for decades and accumulate continuously throughout lifetime. The half-life of lead in the bones has been estimated to be in the range of 10 to 30 years (Ara and Usmani, 2015) while another study (that considered the two types of bones based on the difference in their turnover times) estimated a half-life of 16 years for the cortical bone and 24 years for cortical bones (tibia). The cortical bone has a shorter turnover time than the trabecular bone (Barbosa *et al*., 2005). During pregnancy and lactation, calcium demand increases, leading to bone resorption and the associated release of stored lead into the bloodstream. Bone resorption is of major concern during pregnancy when lead may be transferred across the placenta to the foetus (Rollin *et al*., 2009) and after childbirth, when there is increased risk of exposure in breastfed babies (Rothenberg *et al.*, 2000: Gulson *et al*., 2004). Also, the rate of bone breakdown and formation is increased at childhood, leading to simultaneous increase in the release of bone lead into the blood stream (O'Flaherty, 2000). These make children and women of child-bearing age to be susceptible. Of more concern is the foetus and children being at higher risk of lead poisoning as they are likely to be more affected by lead exposure due to their yet-to-be-developed protective mechanisms and organs. Women exposed to lead are at risk of various complications during pregnancy, including spontaneous abortion and still births (Mandal *et al*., 2022) while adverse health effects such as Attention Deficit Hyperactive Disorders (ADHD) and low Intelligent Quotient (IQ) have been observed in lead-exposed children (Wang *et al*., 2009). This study aims to model the expected blood lead levels in pregnant and lactating women in Osun State, Nigeria who were historically exposed to leaded petrol before its phase-out, compare output with predicted BLLs of subjects born after phase-out and to assess the potential health implications for their offspring.

MATERIALS AND METHODS

A Physiologically Based Kinetic (PBK) model was employed to estimate the blood lead levels in pregnant and lactating women. The PBK model used was earlier developed by the authors and its full description, including the parameters used and its implementation have been previously published (Karokatose *et al*, 2016). The only modification done to the model to achieve the main objective of this study is that only the inhalation route of exposure is considered as shown in figure 1, compared to the inhalation and ingestion route used in the earlier developed model. This is necessary as this study is mainly concerned with the effect of the phase-out of leaded gasoline decades after, on the BLLs of pregnant and lactating women. Data of air lead concentration pre and post phase-out was used to model intake through inhalation. The behavior of lead in the body was reviewed to avoid inclusion of irrelevant organs that were not crucial to the Absorption, Distribution, Metabolism and Excretion (ADME) of lead. Parameters such as bone turnover rates influenced by pregnancy and lactation were also used.

The lung model generated an homogeneous term in the equation which is;

$$D = p \propto$$

Where α is the rate at which lead enters the lungs while p is the proportionality constant (Batchelet et al., 1979). D is the intake quantity from outside the body which helped in modifying the intake rate under different scenarios. 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.

The system of first order differential equation generated (Karokatose, 2016) were solved using Waterloo Maple Software for conducting the simulations. The computational solutions were produced using Maplesoft 2024 and its ODE solver. The model code was verified to satisfy mass balance.

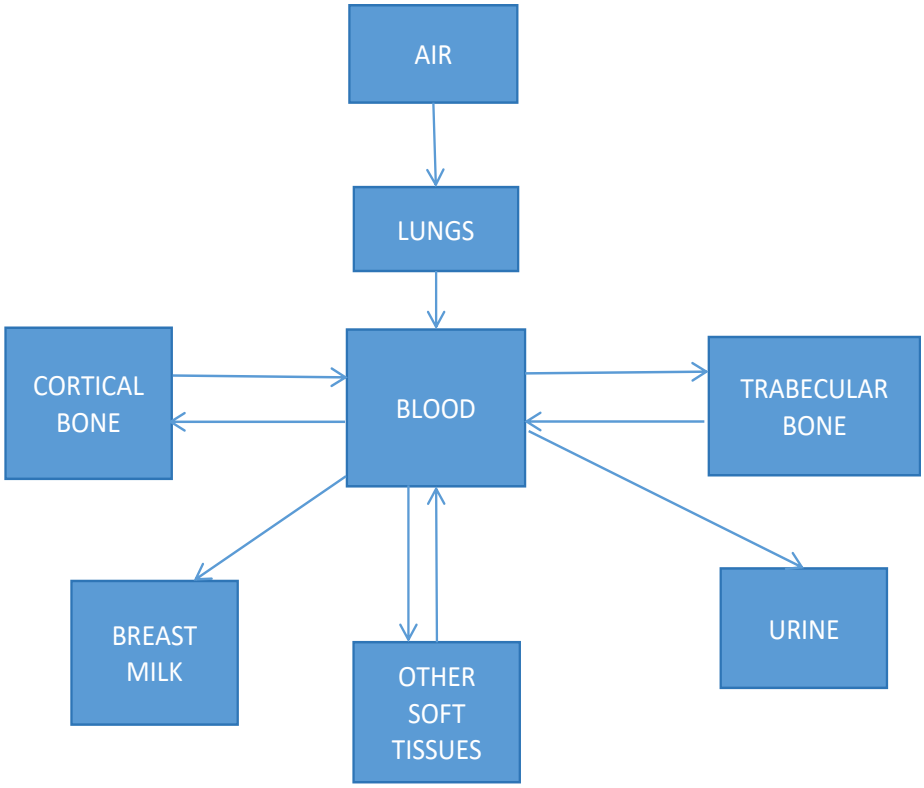

Figure 1: Structure of Lead Model

The Heaviside code was used to modify the intake of lead through air pre and post phase-out of leaded gasoline in 2003. Prior phase-out, the data used for air lead concentration is 38.47μg/m^3 (Obiajunwa et al., 2002) while the data used for post phase-out is 8.09μg/m^3 (Obioh et al., 2005). These data are of interest to the author because the studies were done in Osun State which is the focus of this study. To consider a female child born in 1996, who has been exposed to lead through vehicle exhaust for at least 8 years (approximately 100 months) before the phase-out of leaded gasoline, the model code for the intake rate, D is written as;

$$38.47 * \text{Heaviside}(100 - t) + 8.09 * \text{Heaviside}(t - 100)$$

This means that exposure is reduced from 38.47 to 8.09 after 100 months. This was applied to different scenarios such as children exposed 5 years (60 months) and 3 years (36 months) before phase-out to know their present BLLs both as non-pregnant and pregnant subjects.

Note that the breast milk compartment included does not represent actual breast milk production. It is therefore considered primarily to study the transfer of lead to breast milk post-pregnancy when the model can be adapted to a lactating state.

To model the pregnancy and lactation period, the tissue lead levels of the subjects at 0 days represent the levels at the point of being pregnant at 25 years (300th month in the no pregnancy scenario). For subjects born in 1995, BLL at the inception of pregnancy is 303 μg which is 6.06 μg/dL, assuming a blood volume of 50 dL for the subjects as it has been estimated that the normal blood volume of an adult woman is around 4.3 to 5.0 litres which increases during pregnancy by 30 to 50 % to support the growth of the foetus (Pamela, 2024). Factors such as the age, weight and height also determine blood volume.

Hence, for uniformity, 50 dL and 65 dL (assuming a 30% increase in pregnancy) was used for the no pregnancy and pregnancy scenarios respectively since information about the subjects' age,

weight and height are not known. A subject born in 1998 was predicted to have BLL of 294 µg (5.88 µg/dL) at pregnancy while a subject exposed 3 years before phase-out (born in 2000) has BLL of 292 µg (5.84 µg/dL) at pregnancy. Hence, these values are the starting points (i.e. 0 day) in the pregnancy and lactation simulation output.

RESULTS AND DISCUSSION

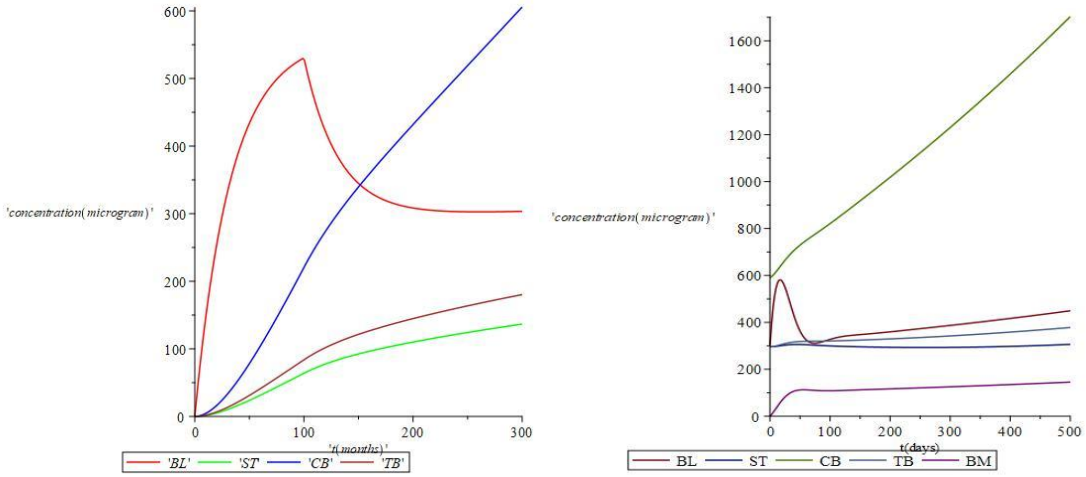

Figure 2: Subjects born in 1995 i.e exposed 8 years before phase-out (Non-Pregnant; Pregnancy and Lactation)

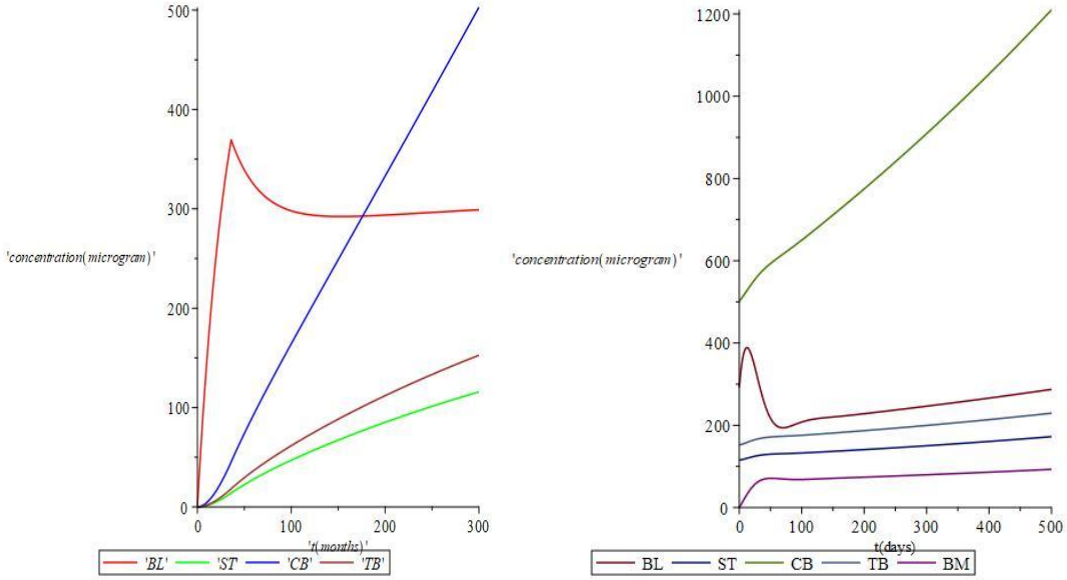

Figure 3: Subjects born in 2000 i.e. exposed 3 years before phase-out (Non-pregnant; Pregnancy and Lactation)

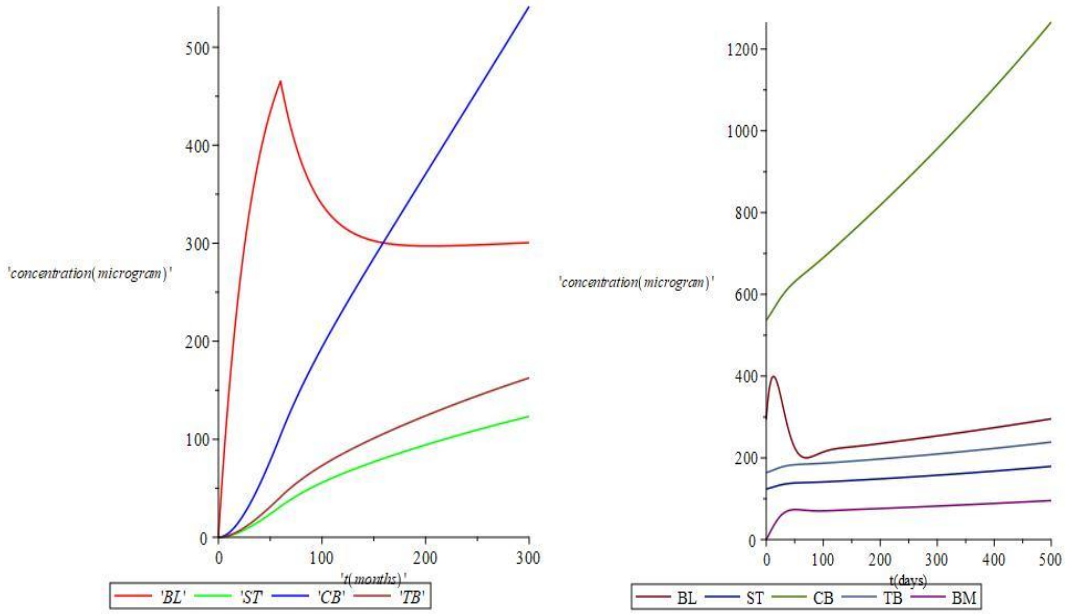

Figure 4: Subjects born in 1998 i.e. exposed 5 years before phase-out (Non-pregnant; Pregnancy and Lactation)

From the simulation outputs, it was predicted that the blood lead levels of a subject born in 1995, 8 years before phase-out was 10.52 µg/dl. This dropped significantly to 6.06 µg/dl by the time the subject is 25 years i.e like 17 years after phase-out and presently still 6.06 µg/dl at 29 years since the pattern evens out. If the same subject decides to get pregnant at 25 years, the BLL increases to 11.54 µg/dl which is about 90.4% increase in pregnancy. This is more than the BLL percentage increase of 26% earlier predicted with the model in 2016 (Karokatose *et al.,* 2016) which may be due to the fact that more lead is stored in the bones during exposure period, giving rise to increase in turnover during physiological changes, especially when the subject is low on calcium. This percentage increase still however agrees with the study done by Hertz and his team who discovered an increase of between 25-99% depending on the age and calcium intake of the women (Hertz et al., 2000). The U-shaped pattern of blood lead level observed in pregnancy as shown if figures 3, 5 and 7 agrees with the observations from studies done by Hertz and Rothenberg (Rothenberg *et al*., 1994; Hertz *et al*., 2000). The pattern may be due to the accessibility of lead stored in bones during pregnancy, particularly and increasingly during the third trimester (Hertz *et al*., 2000). During lactation i.e. beyond 9 months (270 days), the BLL increases to 8.04 µg/dL after a drop from 11.54 µg/dL to 6.26 µg/dL in pregnancy

For subjects exposed for 5 years before the phase-out, the BLLs of such subjects will presently be 5.88µg/dl while the BLLs of the same subjects will increase to 7.98 µg/dl at the onset of pregnancy. A significant drop to 4.9 µg/dl was observed as pregnancy progresses followed by an increase to 5.86µg/dl postpartum which explains the U-pattern of the blood lead levels.

The model also predicted that women exposed 3 years before phase-out will presently have blood lead levels of 5.84µg/dl which is likely to increase to 7.84 µg/dl if pregnant, giving a 34% BLL increase in pregnancy. A drop in BLL was observed towards the end of pregnancy to 4.028 µg/dL. This later increases to 5.68 µg/dL during lactation which gives a 41% increase, confirming that mobilisation of lead from bone is more in lactation than in pregnancy (Karokatose *et al*., 2016; Gulson *et al*., 1998). Thus, putting the infant at potential risk of lead poisoning.

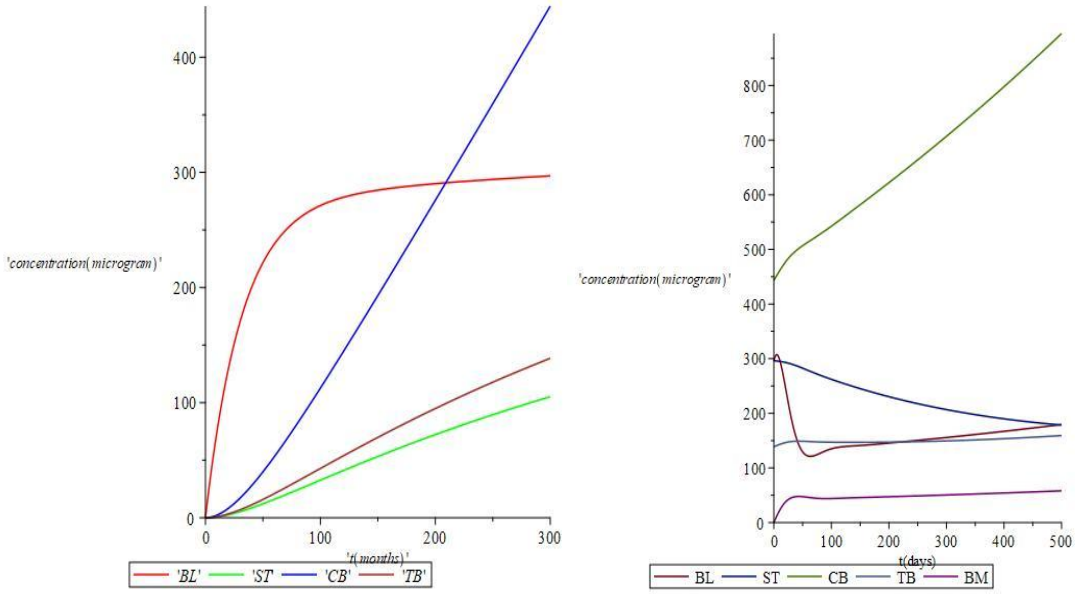

Figure 5: BLL of Subjects born in 2003 (Non-Pregnant, Pregnancy and Lactation)

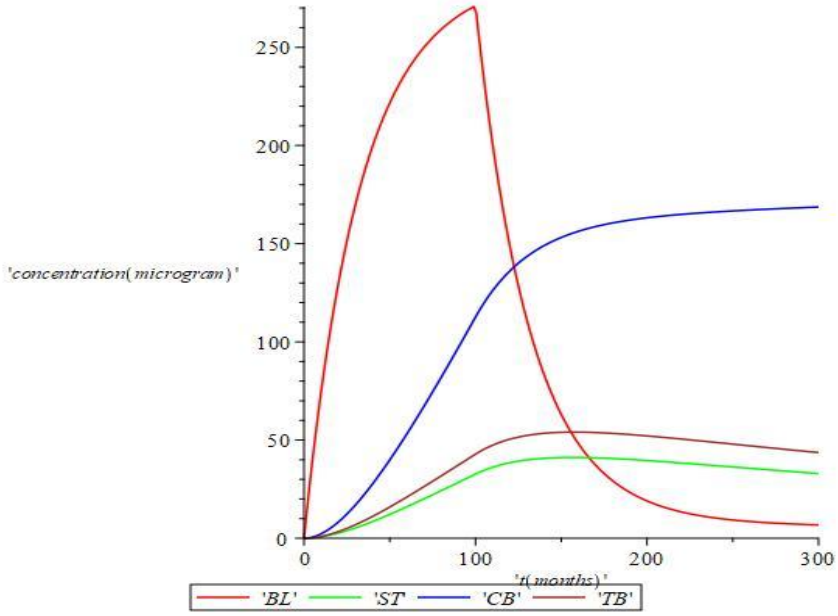

Figure 6: Subjects Born 8 years after phase-out

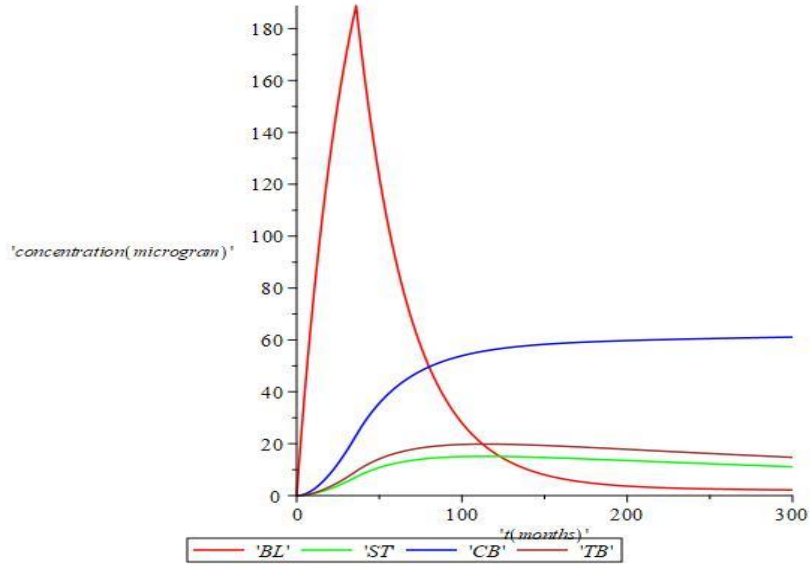

Figure 7: Subjects Born 3 years after Phase-out

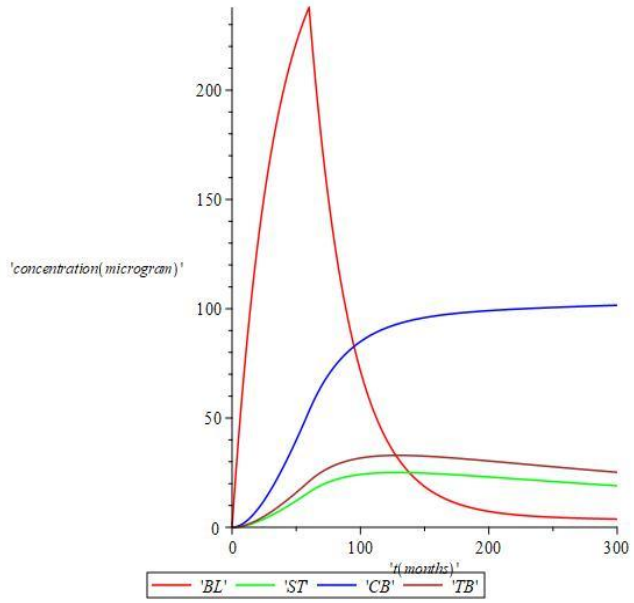

Figure 8: Subjects Born 5 years after Phase-out

Another scenario considered in this study is the blood lead levels of subjects born after the phase-out of leaded gasoline in Nigeria. For women exposed to lead 8 years after phase-out, a drastic drop in blood lead levels was observed to as low as the subjects having 0.1µg/dl BLL presently. Subjects born at the year of phase-out are however likely to presently have an elevated BLL of 5.94µg/dl which may likely be as a result of exposure during pregnancy as it has been found that lead readily crosses the placenta by passive diffusion and has been detected in the fetal brain as early as the first trimester (CDC, 2010). This is also corroborated by the U-shaped pattern observed in the model output. It was however predicted that if the subject gets pregnant now, the increase in BLL would be minimal when compared with subjects exposed before the phase-out (from 5.94µg/dL to 6.12µg/dL). This confirms that human maternal subjects born before the phase-out of leaded gasoline are at higher risk of lead poisoning due to endogenous exposure from bone lead mobilisation. This prediction is supported by a human study done by Miranda *et a*l., in 2010 where

it was found that present maternal blood lead levels more likely result from lead remobilization from historic exposures than ongoing exposures.

For subjects born between 3 years and 5 years after phase-out, the BLLs are predicted to range between 0.14 and 0.16µg/dl which obviously shows that the BLLs of subjects born after phase-out will not pose risk either in pregnancy or lactation as these values tend to zero. It should however be noted that exposure from additional sources, such as dietary intake and occupational exposure were not included in these conservative estimates. Consideration of other exposure sources could cause increase in subjects blood lead levels. That is, the BLL may not be this low if other sources of exposure such as ingestion (through food and water) is considered.

Generally, Model simulations indicate that women who had significant childhood exposure to leaded petrol exhibit blood lead levels above 5 µg/dL during pregnancy and lactation. These levels exceed the recommended intervention threshold by the U.S. Department of Health and Human Services. Hence, this elevated maternal blood lead levels pose risks to the foetus in pregnancy and subsequently the infants through breastfeeding during lactation as a percentage increase in the mobilization of bone lead to blood is more in lactation than in pregnancy (63% as predicted by the 2016 model). This could lead to cognitive deficits, behavioral problems, and reduced IQ scores in children. Tables 1 and 2 below shows the summary of the results both for pre-phase-out and post phase-out.

Table 1: Predicted Blood Lead Levels of Subjects Born before Phase-out at Different Stages

Scenarios	BLL before phase-out (µg/dL)	BLL Presently (µg/dL)	BLL in Pregnancy (µg/dL)	BLL in Lactation (µg/dL)
Exposed 8 years before phase-out (born in 1995)	10.52	6.06	11.54	8.04 (after a drop to 6.26)
Exposed 5 years before phase-out (born in 1998)	9.4	5.88	7.98	5.86 (after a drop to 4.9)
Exposed 3 years before phase-out (born in 2000)	7.4	5.84	7.84	5.68 (after a drop to 4.028)

Table 2: Predicted Blood Lead Levels of Subjects Born after Phase-out

Scenarios	BLL (µg/dL)
Born 8 years after phase-out	0.1
Born 5 years after phase-out	0.14
Born 3 years after phase-out	0.16

CONCLUSION

In conclusion, this study has been able to confirm the persistent effects of historical lead exposure in Osun State, Nigeria and its potential implications for maternal and child health through the use

of a Physiologically-Based Kinetic (PBK) Model. Women aged 25 years and above who were exposed to leaded petrol in their early years are at risk of having elevated blood lead levels during pregnancy and lactation as a result of increase in the release of stored lead in bones during these physiological processes. The findings of the study therefore underscore the need for targeted public health interventions, such as calcium supplementation programs for women in Nigeria who were exposed to leaded petrol during childhood. Subjects with adequate level of blood calcium will not need to source for calcium (and consequently, inadvertently, lead) from the bones. Other interventions like educational campaigns on lead exposure risks and screening initiatives for populations at risk should also be encouraged.

RECOMMENDATIONS

While this study provides a conservative estimate of blood lead levels, additional research incorporating dietary and occupational lead exposures is needed. Also, longitudinal studies tracking blood lead levels in pregnant women over time could further validate our model predictions.

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